Health Evidence Review Commission

January 14, 2016
1:30 PM

Clackamas Community College
Wilsonville Training Center, Room 111-112
29373 SW Town Center Loop E, Wilsonville, Oregon, 97070

Section 1.0

Call to Order

AGENDA

HEALTH EVIDENCE REVIEW COMMISSION

Wilsonville Training Center, Rooms 111-112

January 14, 2016

1:30-4:30 pm

(All agenda items are subject to change and times listed are approximate)

#	Time	Item	Presenter	Action Item
1	1:30 PM	Call to Order	Susan Williams	
2	1:35 PM	Approval of Minutes (November 12, 2015)	Susan Williams	X
3	1:40 PM	Director's Report	Darren Coffman	
4	1.45 PM	Value-based Benefits Subcommittee Report	Ariel Smits Cat Livingston	X
5	2:15 PM	Topic Rescan for 2013 Approved Coverage Guidances • Carotid endarterectomy • Cervical cancer screening • Continuous blood glucose monitoring in diabetes mellitus • Coronary artery calcium scoring • Coronary computed tomography angiography • Diagnosis of sleep apnea in adults • Induction of labor • Management of recurrent acute otitis media in children • MRI for breast cancer diagnosis • Neuroimaging for headache • PET scan for breast cancer • Self-monitoring of blood glucose for type 1 & 2 diabetes • Treatment of attention deficit hyperactivity disorder • Vertebroplasty, kyphoplasty and sacroplasty	Cat Livingston	X
6	3:00 PM	Nitrous oxide use for labor pain management • EbGS Recommended Coverage Guidance • VbBS Recommended Prioritized List Changes	Cat Livingston	X
7	3:20 PM	Indications for Proton Beam Therapy • HTAS Recommended Coverage Guidance • VbBS Recommended Prioritized List Changes	Cat Livingston	X
8	4:20 PM	Next Steps • Schedule next meeting – March 10, 2016 Wilsonville Training Center, Rooms 111-112	Susan Williams	
9	4:30 PM	Adjournment	Susan Williams	

Note: Public comment will be taken on each topic per HERC policy at the time at which that topic is discussed.

Minutes

HEALTH EVIDENCE REVIEW COMMISSION
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
November 12, 2015

Members Present: Som Saha, MD, MPH, Chair; Gary Allen, DMD; Beth Westbrook, PsyD; Wiley Chan, MD; Vern Saboe, DC; Mark Gibson; Leda Garside, RN, MBA; Susan Williams, MD; Gerald Ahmann, MD, PhD; Derrick Sorweide, DO; Mark Gibson; Chris Labhart; Holly Jo Hodges, MD.

Members Absent: Irene Croswell, RPh

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Denise Taray, RN; Jason Gingerich; Daphne Peck.

Also Attending: Kim Wentz, MD, MPH, Brian Nieubuurt (Oregon Health Authority); Erica Pettigrew, MD, Karen Kovak (OHSU); Valerie King, MD MPH, Adam Obley, MD, MPH, Craig Mosbaek (OHSU Center for Evidence Based Policy); Silke Akerson (Oregon Midwifery Council); Sharron Fuchs; Duncan Neilson, MD (Legacy Health); Melissa Cheyney, PhD (OSU); Pam Keuneke (Providence); Laura Jenson (OHSU, American Council of Nurse Midwives).

Call to Order

Som Saha, Chair of the Health Evidence Review Commission (HERC), called the meeting to order and role was called.

Minutes Approval

MOTION: To approve the minutes of the 10-1-2015 meeting as presented. CARRIES 12-0.

Director's Report

Membership
Darren Coffman introduced Gary Allen, DMD, newly appointed dental representative. Dr. Allen is a native Oregonian who served in the military and is currently the dental director at Advantage Dental. He has been involved in many health policy commissions and taskforces over the last two decades and is interested in furthering oral health in Oregon.

At the end of December, some Commissioner's terms are expiring. Mark Gibson (consumer representative) and Dr. Derrick Sorweide (*o*steopathic physician*)* are on track to be reappointed directly. Replacement of Drs. Saboe (complementary and alternative medicine) and Ahmann (oncologist) is delayed; incumbents will continue to attend until replaced. Irene Croswell (retail pharmacists) is leaving

the Commission after an employment change but will remain until another pharmacist can be recruited and appointed.

ICD-10-CM update
Staff have been publishing errata to the ICD-10 list implemented October 1, 2015 every 2 weeks since September. When the January 1, 2016 List is published, any errors that are not straightforward and can't be changed by errata may need to wait until the next interim modification date of October 1, 2016. Staff are working with OHA Health Systems to develop a plan to handle these types of issues. One option proposed is to have a March 1, 2016 List update. Another suggestion is to more liberally define what may be included in an errata.

Biennial review changes related to conditions of the back and spine
Implementation of these biennial changes approved by HERC in March are being delayed by OHA leadership to ensure that rate adjustments accurately reflect projected new costs and savings resulting from these changes in benefits. The January 1, 2016 List will reflect all the changes approved with the exception of these involving conditions of the back and spine, which will be notated clearly in a fashion still being developed by staff. Hodges asked that the new list represent only what it being implemented at that time to the degree possible.

Coverage Guidance Topic: Planned Out-of-hospital birth
Meeting materials, pages 63-226

Dr. Cat Livingston gave a brief summation of the evidence presentation and discussion held at the October 1, 2015 meeting (meeting materials pages 168-173).

Minor changes were made to the box language at the same time the high risk coverage exclusion, transfer and consultation criteria were reorganized into categories according to whether they impact the mother, fetus or placenta.

Jason Gingerich introduced the appointed ad-hoc experts, Duncan Neilson, MD, and Melissa Cheyney, PhD, who assisted the subcommittee as they developed their recommendations, announced their stated conflicts of interest and outlined their role in the process.

Members discussed a mother's known strep Group B status at the time of birth. While very rare, an active infection can pass to the infant with sometimes devastating effects, with a near 50% mortality rate. Some mothers refuse the test and would reject the prophylactic IV antibiotics recommended during labor to prevent the passage of the infection. Cheyney added midwifes are currently taking training to allow IV antibiotics used in home births as that has become part of their scope of practice.

Gibson noted the difficulty of demanding tests for Group B strep, stating if a mother wanted to have an out-of-hospital birth that the test should be completed as well as a risk assessment and informed consent about the pros and cons of the prophylaxis treatment. Only then should a mom be able to say no to antibiotics.

Hodges shared, before 1996, every year 7,500 babies were born through the bacteria and would contract the disease, with half of the infants dying of sepsis.

Saha asked how the situation differed between hospital and an out-of-hospital birth. Duncan explained the baby gets the advantages of a neonatal team dedicate to its care 24/7 with at least a 48 hour stay. At home, midwifes look in at 24 then 48 hours.

Dr. Val King mentioned that approximately 25% of the Medicaid population are Group B strep carriers.

Dr. Kim Wentz added that death or brain damage can occur in the few hours it takes to get IV antibiotics started in a home setting. She further stated surveillance at home cannot be the same as surveillance in the hospital. She also shared the many instances she's seen where true informed consent isn't documented or where patients did not understand the context of the risks.

MOTION: To approve the VbBS recommendation on the requirement of testing for Group B strep carrier status in order to receive coverage for a planned out-of-hospital birth in the guideline note. CARRIES: 11-1 (Opposed: Hodges)

MOTION: To approve the proposed planned out-of-hospital guideline note for the Prioritized List as recommended by VbBS. Carries 12-0.

MOTION: To include the the requirement of testing for Group B strep carrier status in order to receive coverage for a planned out-of-hospital birth in the coverage guidance. CARRIES: 12-0.

MOTION: To approve the proposed coverage guidance for planned out-of-hospital birth as presented, including the recommendations of EbGS and subsequent amendments. (Abstained: Hodges)

Sharron Fuchs offered testimony, thanking the Commission for taking these steps to help ensure newborn safety in an out-of-hospital setting.

Approved Coverage Guidance:

HERC Coverage Guidance

Planned out-of-hospital (OOH) birth is recommended for coverage for women who do not have high-risk coverage exclusion criteria as outlined below *(weak recommendation)*. This coverage recommendation is based on the performance of appropriate risk assessments[1] and the OOH birth attendant's compliance with the consultation and transfer criteria as outlined below.

Planned OOH birth is not recommended for coverage for women who have high risk coverage exclusion criteria as outlined below, or when appropriate risk assessments are not performed, or where the attendant does not comply with the consultation and transfer criteria as outlined below *(strong recommendation)*.

High-risk coverage exclusion criteria:

Complications in a previous pregnancy:

Maternal surgical history

- Cesarean section or other hysterotomy

- Uterine rupture
- Retained placenta requiring surgical removal
- Fourth-degree laceration without satisfactory functional recovery

Maternal medical history

- Pre-eclampsia requiring preterm birth
- Eclampsia
- HELLP syndrome

Fetal

- Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty
- Baby with neonatal encephalopathy
- Placental abruption with adverse outcome

Complications of current pregnancy:

Maternal

- Induction of labor
- Prelabor rupture of membranes > 24 hours

- Pre-existing chronic hypertension; Pregnancy-induced hypertension with diastolic blood pressure greater than or equal to 90 mmHg or systolic blood pressure greater than or equal to 140 mmHg on two consecutive readings taken at least 30 minutes apart
- Unknown group B strep carrier state
- Lack of informed consent on group B strep prophylaxis, if mother is Group B strep positive.
- Eclampsia or pre-eclampsia
- Anemia – hemoglobin less than 8.5 g/dL
- Thrombosis/thromboembolism/ thrombocytopenia (platelets <100,000), or other maternal bleeding disorder
- Drug or alcohol use with high risk for adverse effects to fetal or maternal health
- Maternal mental illness requiring inpatient care
- Unknown or positive HIV, syphilis or Hepatitis B status
- Current active infection of varicella at the time of labor; rubella infection anytime during pregnancy; active infection (outbreak) of genital herpes at the time of labor
- Refractory hyperemesis gravidarum
- Diabetes, type I or II, uncontrolled gestational diabetes, or gestational diabetes controlled with medication

Placental

- Low lying placenta within 2 cm or less of cervical os at term; placenta previa, vasa previa
- Placental abruption/abnormal bleeding
- Recurrent antepartum hemorrhage
- Uteroplacental insufficiency

Fetal

- Gestational age - preterm or postdates (defined as gestational age < 37 weeks + 0 days or > 41 weeks + 6 days)
- Multiple gestation
- Non-cephalic fetal presentation
- IUGR (defined as fetal weight less than fifth percentile using ethnically-appropriate growth tables, or concerning reduced growth velocity on ultrasound)
- Abnormal fetal heart rate/Doppler/surveillance studies
- Oligohydramnios or polyhydramnios
- Blood group incompatibility with atypical antibodies, or Rh sensitization
- Molar pregnancy

Transfer criteria:

If out-of-hospital birth is planned, certain intrapartum and postpartum complications may necessitate transfer to a hospital to meet coverage criteria. For these indications, an attempt should be made to transfer the mother and/or her newborn; however, imminent fetal delivery may delay or preclude actual transfer prior to birth.

Maternal

- Temperature ≥ 38.0 C
- Maternal infection requiring hospital treatment (e.g. endometritis or wound infection)
- Hemorrhage (hypovolemia, shock, need for transfusion)
- Retained placenta > 60 minutes
- Laceration requiring hospital repair (e.g., extensive vaginal, cervical or third- or fourth-degree trauma)
- Enlarging hematoma
- Bladder or rectal dysfunction

Fetal and uteroplacental

- Repetitive or persistent abnormal fetal heart rate pattern
- Thick meconium staining of amniotic fluid
- Prolapsed umbilical cord
- Failure to progress/failure of head to engage in active labor
- Chorioamnionitis or other serious infection (including toxoplasmosis, rubella, CMV, HIV, etc.)
- Uterine rupture, inversion or prolapse

If the infant is delivered out-of-hospital, the following complications require transfer to a hospital for the out-of-hospital birth to meet coverage criteria:

- Low Apgar score (< 5 at 5 minutes, < 7 at 10 minutes)
- Weight less than 5th percentile for gestational age
- Unexpected significant or life-threatening congenital anomalies
- Respiratory or cardiac irregularities, cyanosis, pallor
- Temperature instability, fever, suspected infection or dehydration

- Hyperglycemia/hypoglycemia unresponsive to treatment
- Hypotonia, tremors, seizures, hyperirritability
- Excessive bruising, enlarging cephalohematoma, significant birth trauma
- Vomiting/diarrhea

Consultation criteria:

Certain high risk conditions require consultation (by a provider of maternity care who is credentialed to admit and manage pregnancies in a hospital) for coverage of a planned out-of-hospital birth to be recommended. These complications include (but are not limited to) patients with:

Complications in a previous pregnancy:

Maternal

- More than three first trimester spontaneous abortions, or more than one second trimester spontaneous abortion
- More than one preterm birth, or preterm birth less than 34 weeks 0 days in most recent pregnancy
- Pre-eclampsia, not requiring preterm birth
- Cervical insufficiency/prior cerclage
- Third degree laceration; fourth-degree laceration with satisfactory functional recovery
- Postpartum hemorrhage requiring additional pharmacologic treatment or blood transfusion
- Retained placenta requiring manual removal

Fetal

- Child with congenital and/or hereditary disorder
- Baby > 4.5 kg or 9 lbs 14 oz
- Shoulder dystocia, with or without fetal clavicular fracture
- Unexplained stillbirth/neonatal death or previous death unrelated to intrapartum difficulty
- Unresolved intrauterine growth restriction (IUGR) or small for gestational age (defined as fetal or birth weight less than fifth percentile using ethnically-appropriate growth tables)
- Blood group incompatibility, and/or Rh sensitization

Complications of current pregnancy:

Maternal

- Inadequate prenatal care (defined as less than five prenatal visits or care began in the third trimester)
- Body mass index at first prenatal visit of greater than 35 kg/m^2
- History of maternal seizure disorder (excluding eclampsia)
- Gestational diabetes, diet-controlled
- Maternal mental illness under outpatient psychiatric care with suspicion for psychosis or potential harm to self or infant
- Maternal anemia with hemoglobin < 10.5 g/dL, unresponsive to treatment

- Third-degree laceration not requiring hospital repair
- Laparotomy during pregnancy

Fetal

- Fetal macrosomia (estimated weight >4.5 kg or 9 lbs 14 oz)
- Confirmed intrauterine death
- Life-threatening congenital anomalies (unless non rescucitation planned)
- Family history of genetic/heritable disorders that would impact labor, delivery or newborn care

[1]Risk assessment should be done initially when planning the location of birth and updated throughout pregnancy, labor, and delivery to determine if out-of-hospital birth is still appropriate *(weak recommendation).*

Approved Changes for the Prioritized List of Health Services:

Guideline Note XXX, PLANNED OUT-OF-HOSPITAL BIRTH

Lines 1, 2

Planned out-of-hospital birth is included on these lines when appropriate risk assessments are performed, and the consultation and transfer criteria are followed, and no high risk coverage exclusion criteria exist. Risk assessment should be done initially when planning the location of birth, and updated throughout pregnancy, labor, and delivery to determine if out-of-hospital birth is still appropriate. The clinical and/or diagnostic assessment of each criterion, with the exception of those marked with an asterisk (*), is necessary for planned out-of-hospital birth to be included on these lines. (Criteria marked with an asterisks may not be known or not be pertinent if there is no clinical indication for concern and additional diagnostic testing is not indicated.) An ultrasound is required to rule out certain risk criteria (e.g. multiple gestation, placenta previa, and life threatening congenital anomalies). Certain risk criteria require serial measurements such as fundal height and blood pressure. If a woman refuses a required clinical or diagnostic assessment, then ascertainment of her risk status is unknowable and she does not meet criteria for coverage for an out-of-hospital birth. Documentation of continuing appropriate risk assessment and routine prenatal care is required.

High-risk coverage exclusion criteria:

Complications in a previous pregnancy:

Maternal surgical history

- Cesarean section or other hysterectomy
- Uterine rupture
- Retained placenta requiring surgical removal
- Fourth-degree laceration without satisfactory functional recovery

Maternal medical history

- Pre-eclampsia requiring preterm birth
- Eclampsia
- HELLP syndrome

Fetal and placental

- Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty
- Baby with neonatal encephalopathy

- Placental abruption with adverse outcome

Complications of current pregnancy:

Maternal

- Induction of labor
- Prelabor rupture of membranes > 24 hours
- Pre-existing chronic hypertension; Pregnancy-induced hypertension with diastolic blood pressure greater than or equal to 90 mmHg or systolic blood pressure greater than or equal to 140 mmHg on two consecutive readings taken at least 30 minutes apart
- Unknown group B strep carrier state
- Lack of informed consent on group B strep prophylaxis, if mother is Group B strep positive.
- Eclampsia or pre-eclampsia
- Anemia – hemoglobin less than 8.5 g/dL
- Thrombocytopenia (platelets <100,000)
- Thrombosis/thromboembolism or other maternal bleeding disorder*
- Maternal mental illness requiring inpatient care*
- Drug or alcohol use with high risk for adverse effects to fetal or maternal health
- Unknown, or positive, syphilis, HIV, or Hepatitis B status
- Current active infection of varicella at the time of labor; rubella infection anytime during pregnancy; active infection (outbreak) of genital herpes at the time of labor*
- Refractory hyperemesis gravidarum*
- Diabetes, type I or II, uncontrolled gestational diabetes, or gestational diabetes controlled with medication

Placental

- Low lying placenta within 2 cm or less of cervical os at term; placenta previa, vasa previa
- Placental abruption/abnormal bleeding
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Fetal

- Gestational age - preterm or postdates (defined as gestational age < 37 weeks + 0 days or > 41 weeks + 6 days)
- Multiple gestation
- Non-cephalic fetal presentation
- IUGR (defined as fetal weight less than fifth percentile using ethnically-appropriate growth tables, or concerning reduced growth velocity on ultrasound)*
- Oligohydramnios or polyhydramnios*
- Abnormal fetal heart rate/Doppler/surveillance studies
- Blood group incompatibility with atypical antibodies, or Rh sensitization
- Molar pregnancy

Transfer criteria:

If out-of-hospital birth is planned, certain intrapartum and postpartum complications may necessitate transfer to a hospital to meet coverage criteria. For these indications, an attempt should be made to transfer the mother and/or her newborn; however, imminent fetal delivery may delay or preclude actual transfer prior to birth.

Maternal

- Temperature ≥ 38.0 C
- Maternal infection requiring hospital treatment (e.g. endometritis or wound infection)

- Hemorrhage (hypovolemia, shock, need for transfusion)
- Retained placenta > 60 minutes
- Laceration requiring hospital repair (e.g., extensive vaginal, cervical or third- or fourthdegree trauma)
- Enlarging hematoma
- Bladder or rectal dysfunction

Fetal and uterine

- Repetitive or persistent abnormal fetal heart rate pattern
- Thick meconium staining of amniotic fluid
- Prolapsed umbilical cord
- Failure to progress (as defined by the American Congress of Obstetricians and Gynecologists, March 2014, found at http://www.acog.org/Resources-And-Publications/Obstetric-Care-Consensus-Series/Safe-Prevention-of-the-Primary-Cesarean-Delivery)/failure of head to engage in active labor
- Chorioamnionitis or other serious infection (including toxoplasmosis, rubella, CMV, HIV, etc.)
- Uterine rupture, inversion or prolapse

If the infant is delivered out-of-hospital, the following complications require transfer to a hospital for the out-of-hospital birth to meet coverage criteria:

- Low Apgar score (< 5 at 5 minutes, < 7 at 10 minutes)
- Weight less than 5th percentile for gestational age
- Unexpected significant or life-threatening congenital anomalies
- Respiratory or cardiac irregularities, cyanosis, pallor
- Temperature instability, fever, suspected infection or dehydration
- Hyperglycemia/hypoglycemia unresponsive to treatment
- Hypotonia, tremors, seizures, hyperirritability
- Excessive bruising, enlarging cephalohematoma, significant birth trauma
- Vomiting/diarrhea

Consultation criteria:

Certain high risk conditions require consultation (by a provider of maternity care who is credentialed to admit and manage pregnancies in a hospital) for coverage of a planned out-of-hospital birth to be recommended. These complications include (but are not limited to) patients with:

Complications in a previous pregnancy:

Maternal

- More than three first trimester spontaneous abortions, or more than one second trimester spontaneous abortion
- More than one preterm birth, or preterm birth less than 34 weeks 0 days in most recent pregnancy
- Pre-eclampsia, not requiring preterm birth
- Cervical insufficiency/prior cerclage
- Third degree laceration; fourth-degree laceration with satisfactory functional recovery
- Life-threatening congenital anomalies (unless fatal anomalies with nonresuscitation planned)
- Postpartum hemorrhage requiring additional pharmacologic treatment or blood transfusion
- Retained placenta requiring manual removal

Fetal

- Child with congenital and/or hereditary disorder
- Baby > 4.5 kg or 9 lbs 14 oz
- Shoulder dystocia, with or without fetal clavicular fracture
- Unexplained stillbirth/neonatal death or previous death unrelated to intrapartum difficulty

- Unresolved intrauterine growth restriction (IUGR) or small for gestational age (defined as fetal or birth weight less than fifth percentile using ethnically-appropriate growth tables)
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Complications of current pregnancy:

Maternal

- Inadequate prenatal care (defined as less than five prenatal visits or care began in the third trimester)
- Body mass index at first prenatal visit of greater than 35 kg/m2
- History of maternal seizure disorder (excluding eclampsia)
- Gestational diabetes, diet-controlled
- Maternal mental illness with suspicion for psychosis or potential harm to self or infant under outpatient psychiatric care
- Maternal anemia with hemoglobin < 10.5 g/dL, unresponsive to treatment
- Third-degree laceration not requiring hospital repair
- Laparotomy during pregnancy

Fetal

- Fetal macrosomia (estimated weight >4.5 kg or 9 lbs 14 oz)
- Confirmed intrauterine death
- Family history of genetic/heritable disorders that would impact labor, delivery or newborn care

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Value-based Benefits Subcommittee (VbBS) Report on Prioritized List Changes

Meeting materials, pages 228-329

Ariel Smits, reported that the VbBS met earlier in the day, 11-12-2015. The recommendations are mostly about coding changes.

RECOMMENDED CODE MOVEMENT (effective 1/1/16)

- Add or delete various codes related to straightforward changes
- Add the 2016 CPT and HCPCS codes to various lines/Health Systems Division files
- Add various diagnosis codes to a covered line for conditions which might affect young children placed on foster care or who have otherwise had early childhood trauma
- Add the diagnosis code for Buerger's disease to a covered line and remain on an uncovered line with a new guideline specifying that it is only on the covered line for treatment of ulcers and/or gangrene and does not pair with revascularization procedures

RECOMMENDED GUIDELINE CHANGES (effective 1/1/16)

- Modify the nerve block ancillary guideline to add new 2016 nerve block CPT codes
- Modify the non-prenatal genetic testing guideline to incorporate the current figure D1 (which will be removed), to update NCCN references, to add new BRCA testing CPT codes, to add a section recommending genetic counseling and indicated testing of cancer survivors, to add back a deleted section regarding a cystic fibrosis (CF) testing code, to limit CF testing to once per lifetime, and to move a requirement for the least costly/broad testing which would give the required information
- Modify the prenatal genetic testing guideline to allow panel testing for Ashkenazi Jewish patients, to limit CF testing to the 2 CPT codes most commonly used for this, and to add CPT

codes to the chorionic villus sampling (CVS)/amniocentesis entry to better capture the range of codes intended for coverage

- Modify the hyperbaric oxygen guideline to include all the appropriate ICD-10 codes for diabetic ulcers and gangrene
- Add new guidelines to limit use of 2016 CPT codes, including sclerotherapy, fetal MRI, and genetic testing for cardiac transplant rejection
- Add a new guideline to limit the use of a non-specific conduct disorder diagnosis to children 5 and younger
- Modify the acupuncture guideline to remove the requirement for referrals for non-pregnancy related indications, standardize the number of visits for various conditions to 12 (6 for breach fetal presentation), and correct ICD-10 codes for various conditions
- Modify the tobacco cessation guideline to clarify alignment of the recommended services for coverage with ACA requirements
- Add a new multisector intervention statement regarding tobacco cessation practices
- Tobacco cessation and elective surgery
    - Consider requirement of intensive intervention prior to surgery
    - This will come back later for further consideration

MOTION: To accept the VbBS recommendations on Prioritized List changes not related to coverage guidances, as stated. See the VbBS minutes of 11-12-2015 for a full description. Carries: 12-0.

Coverage Guidance Topic: Proton beam therapy

Meeting materials, pages 330-445

Topic tabled until the January 14, 2016 meeting.

Adjournment

Meeting adjourned at 4:15 pm. Next meeting will be from 1:30-4:30 pm on Thursday, January 14, 2016 at Clackamas Community College Wilsonville Training Center, Rooms 111-112, Wilsonville, Oregon.

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on November 12, 2015

For specific coding recommendations and guideline wording, please see the text of the 11-12-2015 VbBS minutes.

RECOMMENDED CODE MOVEMENT (effective 1/1/16)

- Add or delete various codes related to straightforward coding changes
- Add the 2016 CPT and HCPCS codes to various lines/Health Systems Division files
- Add various diagnosis codes to a covered line for conditions which might affect young children placed on foster care or who have otherwise had early childhood trauma
- Add the diagnosis code for Buerger's disease to a covered line and remain on an uncovered line with a new guideline specifying that it is only on the covered line for treatment of ulcers and/or gangrene and does not pair with revascularization procedures.

RECOMMENDED GUIDELINE CHANGES (effective 1/1/16)

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- Modify the prenatal genetic testing guideline to allow panel testing for Ashkenazi Jewish patients, to limit CF testing to the 2 CPT codes most commonly used for this, and to add CPT codes to the chorionic villus sampling (CVS)/amniocentesis entry to better capture the range of codes intended for coverage.
- Modify the hyperbaric oxygen guideline to include all the appropriate ICD-10 codes for diabetic ulcers and gangrene.
- Add new guidelines to limit use of 2016 CPT codes, including sclerotherapy, fetal MRI, and genetic testing for cardiac transplant rejection.
- Add a new guideline to limit the use of a non-specific conduct disorder diagnosis to children 5 and younger.
- Modify the acupuncture guideline to remove the requirement for referrals for non-pregnancy related indications, standardize the number of visits for various conditions to 12 (6 for breach fetal presentation), and correct ICD-10 codes for various conditions.
- Modify the tobacco cessation guideline to align the recommended services for coverage with ACA requirements
- Add a new guideline for planned out-of-hospital birth based on a new coverage guidance
- Add a new multisector intervention statement regarding tobacco prevention and cessation practices

VALUE-BASED BENEFITS SUBCOMMITTEE
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
November 12, 2015
8:30 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; Susan Williams, MD (via phone until 10:30, then in person); Holly Jo Hodges, MD; Laura Ocker, Lac; Gary Allen, DMD; Mark Gibson (via phone 8:10-10:40, 12:10-end of meeting).

Members Absent: David Pollack, MD; Irene Croswell, RPh.

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Jason Gingerich; Denise Taray, RN; Daphne Peck.

Also Attending: Kim Wentz, MD, MPH, Kirsten Bird, Laurie Theodorou, and Brian Nieubuurt (Oregon Health Authority); Valerie King, MD, MPH, Adam Obley, MD, MPH, Craig Mosbaek (OHSU Center for Evidence Based Policy); Silke Anderson (Oregon Midwifery Council); Duncan Neilsen, MD (Legacy Health); Carole Levanda; Sharron Fuchs; Laura Jenson (OHSU and American Council of Nurse Midwives); Melissa Cheyney, PhD (OSU).

- **Roll Call/Minutes Approval/Staff Report**

  The meeting was called to order at 8:00 am and roll was called. Minutes from the October, 2015 VbBS meeting were reviewed.

  MOTION: To approve the October 1, 2015 minutes as presented. CARRIES 6-0.

  Smits reviewed the errata that have been found since the last meeting. Smits also discussed that HERC staff are actively working on finding a way to incorporate new ICD-10 errata into the Prioritized List in a timely fashion going forward past the January 1, 2016 Prioritized List publication.

  The delay in the implementation in the new back conditions lines was discussed in detail; the back lines approved for January 1, 2016 have been delayed until an unknown future date. HERC staff is planning on publishing a Prioritized List with some type of indication about the older back conditions lines being in place only temporarily. The dental coverage expansion is also temporarily delayed.

  Dr. Gary Allen was introduced and welcomed as the new VbBS dental member. Laura Ocker is unfortunately leaving the VbBS and was thanked for her excellent service.

➢ **Topic: Straightforward/Consent Agenda**

Discussion: There was no discussion about the consent agenda items.

Recommended Actions:

1) Add 33968, 33971 and 33974 (Removal of intra-aortic balloon assist device), 33977 and 33978 (Removal of ventricular assist device; extracorporeal), 33980-33983 (Removal or replacement of ventricular assist device pump(s); implantable intracorporeal) to line 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
2) Remove 44372 (Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, not including ileum; with placement of percutaneous jejunostomy tube) from lines 75 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL, 105 CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION and 383 ESOPHAGEAL STRICTURE; ACHALASIA
    a. Advise Health Systems Division (HSD) to add 44372 to the Ancillary Procedures File
3) Remove 44373 (Small intestinal endoscopy, enteroscopy beyond second portion of duodenum, not including ileum; with conversion of percutaneous gastrostomy tube to percutaneous jejunostomy tube) from lines 105 CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION and 383 ESOPHAGEAL STRICTURE; ACHALASIA
    a. Advise HSD to add 44373 to the Ancillary Procedures File
4) Add Z79.01 (Long term (current) anticoagulation use) to line 285 BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS
5) Change the line title for line 422 DISORDERS OF SHOULDER, INCLUDING SPRAINS/STRAINS GRADE ~~3~~4 THROUGH 6
6) Add Z68.3x (Body mass index (BMI) 30.0-39.9, adult) and Z68.4x (Body mass index (BMI) 40.0+, adult) and Z68.54 (Body mass index (BMI) pediatric, greater than or equal to 95th percentile for age) to lines 325 and 589 OBESITY (ADULT BMI ≥ 30, CHILDHOOD BMI ≥ 95 PERCENTILE) Treatment: Medical and Surgical Care
    a. Advise HSD to remove Z68.3x and Z68.4x and Z68.54 from the Informational Diagnosis File
7) Place 97010 (Application of a modality to 1 or more areas; hot or cold packs) on line 663 MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENT
8) Remove from line 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS and add to line 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE.
    a. I70.20x Unspecified atherosclerosis of native arteries of extremities
    b. I70.29x Other atherosclerosis of native arteries of extremities

c. I70.30x Unspecified atherosclerosis of unspecified type of bypass graft(s) of the extremities
d. I70.39x Other atherosclerosis of unspecified type of bypass graft(s) of the extremities
e. I70.40x Unspecified atherosclerosis of autologous vein bypass graft(s) of the extremities
f. I70.49x Other atherosclerosis of autologous vein bypass graft(s) of the extremities
g. I70.50x Unspecified atherosclerosis of nonautologous biological bypass graft(s) of the extremities
h. I70.59x Other atherosclerosis of nonautologous biological bypass graft(s) of the extremities
i. I70.60x Unspecified atherosclerosis of nonbiological bypass graft(s) of the extremities
j. I70.69x Other atherosclerosis of nonbiological bypass graft(s) of the extremities
k. I70.70x Unspecified atherosclerosis of other type of bypass graft(s) of the extremities
l. I70.79x Other atherosclerosis of other type of bypass graft(s) of the extremities
m. E11.51 Other specified diabetes mellitus with diabetic peripheral angiopathy without gangrene

9) Remove from line 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE and keep on line 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS
   a. I70.21x Atherosclerosis of native arteries of extremities with intermittent claudication
   b. I70.31x Atherosclerosis of unspecified type of bypass graft(s) of the extremities with intermittent claudication
   c. I70.41x Atherosclerosis of autologous vein bypass graft(s) of the extremities with intermittent claudication
   d. I70.51x Atherosclerosis of nonautologous biological bypass graft(s) of the extremities with intermittent claudication
   e. I70.61x Atherosclerosis of nonbiological bypass graft(s) of the extremities with intermittent claudication
   f. I70.71x Atherosclerosis of other type of bypass graft(s) of the extremities with intermittent claudication
   g. I70.22x Atherosclerosis of native arteries of extremities with rest pain
   h. I70.32x Atherosclerosis of unspecified type of bypass graft(s) of the extremities with rest pain
   i. I70.42x Atherosclerosis of autologous vein bypass graft(s) of the extremities with rest pain
   j. I70.52x Atherosclerosis of nonautologous biological bypass graft(s) of the extremities with rest pain

k. I70.62x Atherosclerosis of nonbiological bypass graft(s) of the extremities with rest pain
l. I70.72x Atherosclerosis of other type of bypass graft(s) of the extremities with rest pain
m. I70.26x Atherosclerosis of native arteries of extremities with gangrene
n. I70.36x Atherosclerosis of unspecified type of bypass graft(s) of the extremities with gangrene
o. I70.46x Atherosclerosis of autologous vein bypass graft(s) of the extremities with gangrene
p. I70.56x Atherosclerosis of nonautologous biological bypass graft(s) of the extremities with gangrene
q. I70.66x Atherosclerosis of nonbiological bypass graft(s) of the extremities with gangrene
r. I70.76x Atherosclerosis of other type of bypass graft(s) of the extremities with gangrene

10) Add the following to line 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS and keep on current lines:
    a. E08.52 Diabetes mellitus due to underlying condition with diabetic peripheral angiopathy with gangrene
    b. E10.52 Type 1 diabetes mellitus with diabetic peripheral angiopathy with gangrene
    c. E11.52 Type 2 diabetes mellitus with diabetic peripheral angiopathy with gangrene
11) Add the following to line 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE and keep on current lines
    a. E08.51 Diabetes mellitus due to underlying condition with diabetic peripheral angiopathy without gangrene
    b. E09.51 Drug or chemical induced diabetes mellitus with diabetic peripheral angiopathy without gangrene
    c. E10.51 Type 1 diabetes mellitus with diabetic peripheral angiopathy without gangrene
12) Remove all amputation CPT codes from line 354 NON-LIMB THREATENING PERIPHERAL VASCULAR DISEASE
    a. 24900-24940, 25900-25931, 26910, 26951, 26952, 27025, 27290, 27295, 27590-27598, 27880-28825
13) Remove E08.49, E08.610, E09.49, E09.610, E13.4x, E13.610, E13.618 from line 382 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF- DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION.
14) Remove E08.41, E08.44, E09.41, E09.44, E10.4x, E11.4x, E13.4x (diabetic neuropathy) from line 515 and 541 PERIPHERAL NERVE DISORDERS, medical and surgical therapy

15) Add E08.621, E09.621, E10.621, E13.621, E08.622, E09.622, E10.622, E13.622 (diabetic ulcers) to line 336 ANAEROBIC INFECTIONS REQUIRING HYPERBARIC OXYGEN
    a. Add all codes from these series to GN 107 HYPERBARIC OXYGEN as shown in Appendix A
16) Remove E11.628 (Type 2 diabetes mellitus with other skin complications) from line 336 ANAEROBIC INFECTIONS REQUIRING HYPERBARIC OXYGEN
17) Remove E11.623 from GN107 HYPERBARIC OXYGEN as a non-valid code
18) Remove E11.51 (Type 2 diabetes mellitus with diabetic peripheral angiopathy without gangrene) from line 336 ANAEROBIC INFECTIONS REQUIRING HYPERBARIC OXYGEN
    b. Modify GN107 HYPERBARIC OXYGEN to reflect this change as shown in Appendix A
19) Add E08.52, E09.52, E10.52, E13.52 (diabetic gangrene) to line 336 ANAEROBIC INFECTIONS REQUIRING HYPERBARIC OXYGEN
    c. Add code series to GN107 HYPERBARIC OXYGEN as shown in Appendix A

The following recommended changes are to the new lines involving conditions of the back and spine that are being delayed and will take effect when that delay is lifted:

1) Add 99291-99292 (Critical care, evaluation and management of the critically ill or critically injured patient) to lines 351 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS, 366 SCOLIOSIS, and 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
2) Advise HSD to remove M54.3x (Sciatica) and M54.4x (Lumbago) from the Diagnostic Workup File as they are currently on line 407 CONDITIONS OF THE BACK AND SPINE
3) Remove M41.xx series (Scoliosis) from line 407 CONDITIONS OF THE BACK AND SPINE. Keep only on line 366 SCOLIOSIS.
4) Add line 366 SCOLIOSIS to Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE

MOTION: To approve the recommendations stated in the consent agenda. CARRIES 6-0.

- **Topic: 2016 CPT/HCPCS code review**

Discussion: Most code placements and guideline changes were approved as recommended in the meeting materials with no or minimal discussion. Of note, some of the new codes were discussed previously at the October, 2015 VBBS meeting. Specific codes which had substantive discussion at the current meeting were:

61650-61651 (Endovascular intracranial prolonged administration of pharmacologic agent(s) other than for thrombolysis, arterial, including catheter placement diagnostic angiography, and imaging guidance) were suggested for lines on the Prioritized List based on older code placement. However, VbBS did not feel that there was evidence to support the use of these codes and instead placed these codes on the Services Recommended for Non-Coverage Table. Additionally, it was mentioned that the use of this procedure for treatment of CNS/brain cancers is controversial. These codes can be re-evaluated if providers request review and provide evidence of effectiveness.

78265 Gastric emptying study with small bowel transit and **78266** Gastric emptying study with small bowel and colon transit, multiple days were discussed. VBBS members agreed with placement of 78266 on the Services Recommended for Non-Coverage Table; however, members also felt that 78265 should not be placed on the Diagnostic List, but should be on the Services Recommended for Non-Coverage Table as well.

81432-81433 (Breast and ovarian cancer syndrome testing) were discussed. There was considerable discussion regarding coverage of panels versus BRCA genes alone. The VbBS felt that the panels contained many genetic mutations without evidence that finding these mutations would be meaningful or would affect treatment plans or monitoring. The group decided to only cover the BRCA mutation code (81162) and to place the panels (81432-81433) on the Services Recommended for Non-Coverage Table. These codes were not added to the Non-Prenatal Genetic Testing Guideline as had been suggested in the meeting materials.

The prenatal genetic testing guideline was further modified to include CPT codes used for CVS and amniocentesis. HERC staff will need to further evaluate the CPT codes used for amniocentesis and CVS and will ensure that these codes are complete and will bring back to a future meeting.

Recommended Actions:

1) Approve 2016 CPT code placements as shown in Appendix B
2) Modify Ancillary Guideline A1 as shown in Appendix A
3) Add ICD-10 T88.8xx (Other specified complications of surgical and medical care, not elsewhere classified) to line **428** COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
    - Advise HSD to remove T88.8xx from the Diagnostic Workup File
4) Move E04.1 (Nontoxic single thyroid nodule) from line **656** ENDOCRINE AND METABOLIC CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY to line **634** CYST, HEMORRHAGE, AND INFARCTION OF THYROID
5) Adopt a new guideline regarding sclerotherapy for fluid collection as shown in Appendix C
6) Adopt a new guideline regarding fetal MRI as shown in Appendix C

7) Modify the prenatal and non-prenatal genetic testing guidelines as shown in Appendix A
8) Adopt a new guideline regarding use of the marker test for cardiac transplant rejection as shown in Appendix C

MOTION: To recommend the code and guideline note placements/adoption/ changes as presented or modified. CARRIES 6-0.

- **Topic: Adjustment disorder**

Discussion: Smits reviewed the meeting materials. There was clarification that the current conduct disorders line is limited to children 18 and younger; therefore, the new guideline was modified to remove the reference to adults.

Recommended Actions:

1) Delete the coding specification from line 449 ADJUSTMENT DISORDERS
2) Delete Z71.89 (Other specified counseling) from line 449 ADJUSTMENT DISORDERS
    a. Advise HSD to add Z71.89 to the Informational Diagnosis File
3) Add Z62.8x (Parent-child conflict) and Z63.8 (Other specified problems related to primary support group) and F98.9 (Unspecified behavioral and emotional disorders with onset usually occurring in childhood and adolescence) to line 449 ADJUSTMENT DISORDERS
    a. Advise HSD to remove Z62.8x and Z63.8 from the Informational Diagnosis File
    b. Advise HSD to remove F98.9 from the Unspecified File
4) Add F91.9 (Conduct disorder, unspecified) to line 425 OPPOSITIONAL DEFIANT DISORDER and keep on line 483 CONDUCT DISORDER, AGE 18 OR UNDER
5) Adopt a new guideline limiting the use of F91.9 to children 5 and younger as shown in Appendix C

MOTION: To recommend the code and adoption of the new guideline note as modified. CARRIES 6-0.

- **Topic: Thromboangiitis obliterans**

Discussion: There was minimal discussion of this topic. It was stressed that the intention was that medications and/or other therapies to directly treat Buerger's disease are not intended for coverage on the upper line, as only smoking cessation is effective for treatment of the underlying disease. The placement on the upper line is only for treatment of complications of the disease such as ulcers and gangrene, not for treatment of the actual Buerger's disease itself.

Recommended Actions:

1) Add ICD-10 I73.1 (Buerger's disease) to line 240 LIMB THREATENING VASCULAR DISEASE, INFECTIONS, AND VASCULAR COMPLICATIONS and keep on line 657

CARDIOVASCULAR CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY

2) Adopt a new guideline note for Buerger's disease as shown in Appendix C

MOTION: To recommend the code and new guideline note adoption as presented. CARRIES 6-0.

- **Topic: Acupuncture guideline**

Discussion: Smits reviewed the meeting materials. Williams expressed concern about removing the requirement for referral for acupuncture, feeling that the PCP should be involved to help coordinate care. Ocker replied that the referral requirement delays care, and that some PCPs are not aware of this as an effective treatment and may not offer it when it is appropriate. Olson asked if there is a concern that acupuncture is overused or abused; the response was that this was not entirely clear but abuse potential was probably low. Ocker noted that acupuncturists are required to submit prior authorization for visits beyond the first visit, so therefore appropriateness of diagnosis and utilization could be controlled. The general consensus was that the referral requirement could be removed.

There was further discussion about the number of covered visits allowed for treatment of breech fetal presentation. The proposed 12 visits was felt to be too high. The group felt that 6 visits should be adequate for treatment of this condition.

Recommended Actions:

1) Modify the acupuncture guideline as shown in Appendix A

MOTION: To recommend the guideline note changes as presented. CARRIES 5-1 (Opposed: Williams).

- **Topic: Tobacco prevention and cessation coverage**

Discussion: Livingston reviewed the meeting materials. There was minimal discussion. The reference to the Patient Protection and Affordable Care Act in the proposed guideline was changed to the complete name of the law.

Recommended Actions:

1) Modify Guideline Note 4 regarding tobacco cessation coverage as shown in Appendix A
2) Add a new multisector intervention statement for tobacco cessation as shown in Appendix D

3) Modify the treatment description of line 5 TOBACCO DEPENDENCE Treatment: MEDICAL THERAPY/~~BRIEF~~ BEHAVIORAL COUNSELING ~~NOT TO EXCEED 10 FOLLOW-UP VISITS OVER 3 MONTHS~~

MOTION: To recommend the code and guideline note changes and new guideline note adoption as presented. CARRIES 6-0.

- **Topic: Tobacco use and elective surgery**

Discussion: Livingston reviewed the meeting materials. There was discussion about requiring tobacco cessation prior to penile erectile dysfunction procedures. It was pointed out that these procedures are not on a covered line, but such procedures might be covered through the comorbidity rule. With regard to all elective surgeries, Williams suggested requiring cessation rather than just have an intervention prior to elective surgery as is required in the current prosed guideline. Livingston reviewed that the evidence supports the intervention alone may be successful in improving outcomes, and there was a discussion about whether requiring cessation prior to elective surgery was an overly arduous (versus appropriate) pre-surgical requirement. Olson felt that proposed guideline needs be further wordsmithing and recommended having QHOC review it.

The decision was to delay a decision on the proposed guideline until a future meeting.

Recommended Actions:

1) This topic will be reviewed further and brought back to a future meeting.

- **Topic: Coverage Guidance—Planned out of hospital births**

Discussion: Livingston reviewed the changes made to the proposed Prioritized List guideline, based on the October VbBS meeting discussion. Concerns have been raised in the interim repeatedly about the lack of inclusion of Group B strep (GBS) screening or positivity. There was an extensive discussion about GBS carrier status and whether or not it is appropriate to be a criteria included in the list guideline. And if it is, whether it should include positivity alone, positivity with inadequate prophylaxis, unknown GBS carrier status, or refusal of antibiotics when indicated.

There was public testimony received from Silke Akerson, representing the Oregon Midwifery Council. She stated that inclusion of group B strep (GBS) as a criteria for noncoverage would have a major impact on informed choice and informed refusal. That making treatment of GBS positivity would require provision of IV antibiotics in order for the birth to be covered. She also described enhance monitoring by midwives when mom is a GBS carrier, in which babies are more closely monitored, they see all patients within the first 24 hours after delivery, and they provide focused education about monitoring the baby to the parents. She is especially concerned about the term

"adequate prophylaxis," given that a precipitous delivery may make prophylaxis inadequate, when all involved were trying to do the right thing by providing antibiotics. Akerson also informed the subcommittee that guidance on GBS is not in rule. Midwives just got training on the CDC GBS Guidelines from 2010. Management of GBS was just recently added to scope of practice.

The discussion included an acknowledgement that knowing GBS carrier status was important in order to determine if prophylaxis was indicated, as well as the need for enhanced monitoring.

Akerson's further testimony included that she was pleased with the coverage guidance in general. Additional detailed points of concern included maternal anemia with hemoglobin <10.5. She stated this is a frequent occurrence, and they easily recommend iron rich foods and supplements, and consult and refer a patient if it doesn't resolve. The subcommittee decided to modify it by adding "unresponsive to treatment" to the consultation criteria "maternal anemia with hemoglobin < 10.5 g/dL."

The next point of discussion was around some of the subtypes of infection included in the maternal transfer criteria. Urinary tract infection (UTI) and breast infection rarely occur in the intrapartum setting, and postpartum or antepartum infection could potentially be managed in the outpatient primary care setting, rather than requiring a hospital transfer. It was thought the key pertinent infections were: Maternal infection requiring hospital treatment (e.g. endometritis or wound infection).

Next, the subcommittee discussed the issue of "failure to progress" as being a vague description. Thus ensued a lengthy discussion about the challenge of defining failure to progress and that there are changing definitions within the obstetric literature as well. There were strong preferences to have a clear, available, and consistent definition of failure to progress. The subcommittee settled on referring to the recent ACOG (2014) standards as described in: http://www.acog.org/Resources-And-Publications/Obstetric-Care-Consensus-Series/Safe-Prevention-of-the-Primary-Cesarean-Delivery)

The last two criteria which Akerson had raised potential concern over were: history of a baby over 9 lbs 4 oz, and BMI >35. After a brief discussion, the subcommittee decided to make no changes to the current recommendations.

Recommended Actions:

1) Adopt a new guideline for planned out-of-hospital birth as shown in Appendix C.

MOTION: To approve the recommended changes to the Prioritized List with modifications as shown in Appendix C, based on the draft Planned Out-of-Hospital Birth coverage guidance scheduled for review by HERC at their November 12, 2015 meeting. CARRIES 5-1 (Opposed: Hodges).

- **Topic: Coverage Guidance—Indications for proton beam therapy**

  Discussion: This topic was tabled to the next VBBS meeting.

- **Public Comment:**

  No additional public comment was received.

- **Issues for next meeting:**
  - Tobacco cessation and elective surgeries
  - Coverage Guidance for Indications for proton beam therapy
  - Review placement of vestibular tests
  - Review all intestinal motility studies including wireless capsule endoscopy
  - Intra-arterial balloon angioplasty and intracranial intravascular stenting
  - Modifications to the prenatal testing guideline for CPT codes for use for CVS and amniocentesis
  - MRI for low back conditions guideline
  - Barrett's esophagus and esophageal dysplasia
  - Anemia due to disease
  - Review coverage of PT modalities

- **Next meeting:**

  January 14, 2016 at Clackamas Community College, Wilsonville Training Center, Wilsonville Oregon, Rooms 111-112.

- **Adjournment:**

  The meeting adjourned at 1:43 PM.

Appendix A
Revised Guideline Notes Effective January 1, 2016

ANCILLARY GUIDELINE A1, NERVE BLOCKS

The Health Evidence Review Commission intends that single injection and continuous nerve blocks (CPT 64400-64450, 64461-64463) should be covered services if they are required for successful completion of perioperative pain control for, or post-operative recovery from a covered operative procedure when the diagnosis requiring the operative procedure is also covered. Additionally, nerve blocks are covered services for patients hospitalized with trauma, cancer, or intractable pain conditions, if the underlying condition is a covered diagnosis.

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

~~Coverage of genetic testing in a non-prenatal setting shall be determined by the algorithm shown in Figure C.1 unless otherwise specified below.~~

A) Genetic tests are covered as diagnostic, unless they are listed below in section F1 as excluded or have other restrictions listed in this guideline. To be covered, initial screening (e.g. physical exam, medical history, family history, laboratory studies, imaging studies) must indicate that the chance of genetic abnormality is > 10% and results would do at least one of the following:
    1) Change treatment,
    2) Change health monitoring,
    3) Provide prognosis, or
    4) Provide information needed for genetic counseling for patient; or patient's parents, siblings, or children
B) Pretest and posttest genetic counseling is required for presymptomatic and predisposition genetic testing. Pretest and posttest genetic evaluation (which includes genetic counseling) is covered when provided by a suitable trained health professional with expertise and experience in genetics.
    1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.
C) A more expensive genetic test (generally one with a wider scope or more detailed testing) is not covered if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.
D) Related to genetic testing for patients with breast/ovarian and colon/endometrial cancer or other related cancers suspected to be hereditary, or patients at increased risk to due to family history.
    1) Services are provided according to the Comprehensive Cancer Network Guidelines.
        a) Lynch syndrome (hereditary colorectal, endometrial and other cancers associated with Lynch syndrome) services (CPT 81288, 81292-81300, 81317-

81319, 81435, 81436) and familial adenomatous polyposis (FAP) services (CPT 81201-81203) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Colorectal V.~~2~~1.2014~~5~~ (~~5/19/14~~ 5/4/15). www.nccn.org.

b) ~~BRCA1/BRCA2~~ Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217) for women without a personal history of breast, ovarian and other associated cancers should be provided to high risk women as defined by the US Preventive Services Task Force or according to the NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. V2.2014~~5~~5 (~~9/23/2014~~ 6/25/15). www.nccn.org.

c) ~~BRCA1/BRCA2~~ Breast and ovarian cancer syndrome genetic testing services (CPT 81162, 81211-81217) for women with a personal history of breast, ovarian, and other associated cancers and for men with breast cancer should be provided according to the NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V2.2014~~5~~5 (~~9/23/2014~~ 6/25/15). www.nccn.org.

d) PTEN (Cowden syndrome) services (CPT 81321-81323) should be provided as defined by the NCCN Clinical Practice Guidelines in Oncology. Colorectal Screening. V.1.2013~~5~~5 (~~5/13/13~~ 5/1/15). www.nccn.org.

2) Genetic counseling should precede genetic testing for hereditary cancer whenever possible.

a) Pre and post-test genetic counseling should be covered when provided by a suitable trained health professional with expertise and experience in cancer genetics. Genetic counseling is recommended for cancer survivors when test results would affect cancer screening.

i) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.

b) If timely pre-test genetic counseling is not possible for time-sensitive cases, appropriate genetic testing accompanied by pre- and post- test informed consent and post-test disclosure performed by a board-certified physician with experience in cancer genetics should be covered.

i) Post-test genetic counseling should be performed as soon as is practical.

3) If the mutation in the family is known, only the test for that mutation is covered. For example, if a mutation for BRCA 1 has been identified in a family, a single site mutation analysis for that mutation is covered (CPT 81215), while a full sequence BRCA 1 and 2 (CPT 81211) analyses is not. There is one exception, for individuals of Ashkenazi Jewish ancestry with a known mutation in the family, the panel for Ashkenazi Jewish BRCA mutations is covered (CPT 81212).

4) Costs for rush genetic testing for hereditary breast/ovarian and colon/endometrial cancer is not covered.

E) Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index <70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:
   1) CPT 81228, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
   2) CPT 81229, Cytogenomic constitutional microarray analysis for copy number variants for chromosomal abnormalities; plus cytogenetic constitutional microarray analysis for single nucleotide polymorphism (SNP) variants for chromosomal abnormalities: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder; only if (a) consanguinity and recessive disease is suspected, or (b) uniparental disomy is suspected, or (c) another mechanism is suspected that is not detected by the copy number variant test alone.
   3) CPT 81243, 81244, Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.
   4) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged.

F) Related to other tests with specific CPT codes:
   1) The following tests are not covered:
      a) CPT 81225, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
      b) CPT 81226, CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN).
      c) CPT 81227, CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
      d) CPT 81287, MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis

e) CPT 81291, MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
f) CPT 81330, SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
g) CPT 81350, UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
h) CPT 81355, VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)
i) CPT 81417, re-evaluation of whole exome sequencing
j) CPT 81425-81427, Genome sequence analysis
k) CPT 81470, 81471, X-linked intellectual disability (XLID) genomic sequence panels
l) CPT 81504, Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores

2) The following tests are covered only if they meet the criteria in section A above ~~for the Non-Prenatal Genetic Testing Algorithm~~ AND the specified situations:
   a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
   b) Diagnostic testing for cystic fibrosis (CF)
      i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81223, 81222: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
   c) Carrier testing for cystic fibrosis
      i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered once in a lifetime.
   d) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility): Covered only after genetic counseling.
   e) CPT 81240. F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing

should not be covered for adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

f) CPT 81241. F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

g) CPT 81256, HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D): Covered for diagnostic testing of patients with elevated transferrin saturation or ferritin levels. Covered for predictive testing ONLY when a first degree family member has treatable iron overload from HFE.

h) CPT 81221 SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Generic testing or the anpha-1 phenotype test is appropriate is the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.

i) CPT 81415-81416, exome testing: A genetic counseling/geneticist consultation is required prior to ordering test

j) CPT 81430-81431, Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel: Testing for mutations in GJB2 and GJB6 need to be done first and be negative in non-syndromic patients prior to panel testing.

k) CPT 81440, 81460, 81465, mitochondrial genome testing: A genetic counseling/geneticist or metabolic consultation is required prior to ordering test.

l) CPT 81412 Ashkenazi Jewish carrier testing panel: panel testing is only covered when the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing.

~~m) Do not cover a more expensive genetic test (generally one with a wider scope or more detailed testing) if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.~~

Appendix A
Revised Guideline Notes Effective January 1, 2016

* American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. 2008 Edition, Revised 3/2011 and found at https://www.acmg.net/StaticContent/SGs/CFTR%20Mutation%20Testing.pdf

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING

The following types of prenatal genetic testing and genetic counseling are covered for pregnant women:

1. Genetic counseling (CPT 96040, HPCPS S0265) for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect.
2. Genetic counseling (CPT 96040, HPCPS S0265) prior to consideration of CVS, amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
3. Validated questionnaire to assess genetic risk in all pregnant women
4. Screening high risk ethnic groups for hemoglobinopathies (CPT 83020, 83021)
5. Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency] (CPT 76813, 76814, 81508-81511)
6. Cell free fetal DNA testing (CPT 81507) for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).
7. Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)
8. CVS or amniocentesis (CPT 59000, 59015, 88235, 88269, 88285, 82106, 88280, 88267) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
9. Array CGH (CPT 81228) when major fetal congenital anomalies apparent on imaging, and karyotype is normal
10. FISH testing (CPT 88271, 88275) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
11. Screening for Tay-Sachs carrier status (CPT 81255) in high risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
12. Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-8122224)
13. Screening for fragile X status (CPT 81243, 81244) in patients with a personal or family history of
    a. fragile X tremor/ataxia syndrome
    b. premature ovarian failure
    c. unexplained early onset intellectual disability
    d. fragile X intellectual disability
    e. unexplained autism through the pregnant woman's maternal line

14. Screening for spinal muscular atrophy (CPT 81401) once in a lifetime
15. Screening those with Ashkenazi Jewish heritage for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255). Ashkenazi Jewish carrier panel testing (CPT 81412) is covered if the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing.
16. Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

1. Serum triple screen
2. Screening for thrombophilia in the general population or for recurrent pregnancy loss
3. Expanded carrier screening which includes results for conditions not explicitly recommended for coverage

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-prenatal-genetic.aspx

GUIDELINE NOTE 4, TOBACCO DEPENDENCE

Line 5

~~Persons are eligible for tobacco dependence counseling if a documented quit date has been established.~~ Pharmacotherapy and behavioral counseling are included on this line, alone or in combination, for at least 2 quit attempts per year. A minimum of four counseling sessions of at least 10 minutes each (group or individual, telephonic or in person) are included for each quit attempt. More intensive interventions and group therapy are likely to be the most effective behavioral interventions.

Inclusion on this line follows the minimum standard criteria as defined in the Oregon Public Health Division "Standard Tobacco Cessation Coverage" based on the Patient Protection and Affordable Care Act), available here: https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Pages/pubs.aspx

For January 1, 2016 Prioritized List, but referencing October 1, 2015 back lines due to implementation delay.

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1, 20~~7~~8,374, 41~~4~~5, 46~~8~~7,545, 54~~6~~3

Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:

Line 1 PREGNANCY
Acupuncture pairs on Line 1 for the following conditions and codes.

Hyperemesis gravidarum

ICD-10-CM code: O21.0, O21.1

Acupuncture pairs with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to ~~2~~ 12 sessions of acupressure/acupuncture.

Breech presentation

ICD-10-CM code: O32.1xx0, O32.8xx0

Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to ~~2~~ 6 visits.

Back and pelvic pain of pregnancy

ICD-10-CM code: O33.0

Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions.

Line 20~~7~~8 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE

Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to ~~15~~ 12 total sessions, with documentation of meaningful improvement.

From October 1, 2015 Prioritized List Line 374 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Acupuncture is included on Line 374 only for pairing with disorders of the spine with myelopathy and/or radiculopathy represented by the diagnosis codes G83.4, ~~M47.1x,~~ M47.2x, M50.0x, M50.1x, M51.0x, M51.1x, M54.1x) ~~with referral,~~ for up to 12 sessions.

Line 41~~4~~5 MIGRAINE HEADACHES

Acupuncture pairs on Line 41~~4~~5 for ~~G43.9~~ Migraine (ICD-10-CM code G43.0xx, G43.1xx, G43.5xx, G43.7xx, G43.8xx, G43.9xx), ~~when referred,~~ for up to 12 sessions.

Line 46~~8~~7 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 46~~8~~7 for osteoarthritis of the knee only (ICD-10 code M17.xx) ~~, when referred,~~ for up to 12 sessions.

* F*rom October 1, 2015 Prioritized List* Line 545 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT

Acupuncture pairs on Line 545 with the low back diagnoses (ICD-10-CM codes ~~G83.4, M47.1x, M47.2x, M50.0x, M50.1x, M51.1x, M54.1x~~, M51.36, M51.86, M54.5, M99.03,S33.5xxx, S33.9xxx, S39.092x,S39.82xx, S39.92xx), ~~when referred,~~ for up to 12 sessions. Acupuncture pairs with chronic (>90 days) neck pain diagnoses (ICD-10-CM M53.82, M54.2, S13.4XXX, S13.8XXX) ~~, when referred~~, for up to 12 sessions.

*Line 54~~6~~3 TENSION HEADACHES

Acupuncture is included on Line 54~~6~~3 for treatment of tension headaches (ICD-10-CM G44.2x) ~~, when referred,~~ for up to 12 sessions.

The development of this guideline note was informed by a HERC evidence-based guideline. See http://www.oregon.gov/oha/herc/Pages/blog-low-back-non-pharmacologic-intervention.aspx

*Below the current funding line.

Appendix A
Revised Guideline Notes Effective January 1, 2016

For future Prioritized List with back line changes when implemented.

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1, 20~~78~~,~~374,~~ 407, 41~~4~~5, 46~~8~~7,~~545,~~ 54~~6~~3

Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:

Line 1 PREGNANCY

Acupuncture pairs on Line 1 for the following conditions and codes.

Hyperemesis gravidarum

ICD-10-CM code: O21.0, O21.1

Acupuncture pairs with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to ~~2~~ 12 sessions of acupressure/acupuncture.

Breech presentation

ICD-10-CM code: O32.1xx0, O32.8xx0

Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to ~~2~~ 6 visits.

Back and pelvic pain of pregnancy

ICD-10-CM code: O33.0

Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions.

Line 20~~7~~8 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE

Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to ~~15~~ 12 total sessions, with documentation of meaningful improvement.

Line 407 CONDITIONS OF THE BACK AND SPINE

Acupuncture is included on line 407 for pairing with visit limitations as in GUIDELINE NOTE XXX, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE

Line 41~~4~~5 MIGRAINE HEADACHES

Acupuncture pairs on Line 41~~4~~5 for ~~G43.9~~ Migraine (ICD-10-CM code G43.0xx, G43.1xx, G43.5xx, G43.7xx, G43.8xx, G43.9xx)~~, when referred,~~ for up to 12 sessions.

Line 46~~8~~7 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 46~~8~~7 for osteoarthritis of the knee only (ICD-10 code M17.xx)~~, when referred,~~ for up to 12 sessions.

*Line 54~~6~~3 TENSION HEADACHES

Acupuncture is included on Line 54~~6~~3 for treatment of tension headaches (ICD-10-CM G44.2x)~~, when referred,~~ for up to 12 sessions.

The development of this guideline note was informed by a HERC evidence-based guideline. See http://www.oregon.gov/oha/herc/Pages/blog-low-back-non-pharmacologic-intervention.aspx

*Below the current funding line.

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GUIDELINE NOTE 107, HYPERBARIC OXYGEN

Lines 336,373

Hyperbaric oxygen is a covered service only under the following circumstances:

- when paired with ICD-10-CM codes ~~E11.5x~~ and ~~E11.621, E11.622 and E11.623~~ E08.52, E09.52, E10.52, E11.52,E13.52, E08.621, E09.621, E10.621, E11.621, E13.621, E08.622, E09.622, E10.622, E11.622, E13.622 for diabetic wounds with gangrene OR diabetic wounds of the lower extremities in patients who meet the all of the following criteria:
    - Patient has Type 1 or Type 2 diabetes and has a lower extremity wound that is due to diabetes, AND
    - Patient has a wound classified as Wagner grade III or higher, AND
    - Patient has failed an adequate course of standard wound therapy including arterial assessment, with no measurable signs of healing after at least thirty days, AND
    - Wounds must be evaluated at least every 30 days during administration of hyperbaric oxygen therapy. Continued treatment with hyperbaric oxygen therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.
- when paired with ICD-10-CM codes M27.8 for osteoradionecrosis of the jaw only
- when paired with ICD-10-CM codes O08.0, M60.000-M60.09 only if the infection is a necrotizing soft-tissue infection
- when paired with ICD-10 CM codes S07.xxx,S17.xxx,S38.xxx,S47.1xxA-S47.1xxD,S47.2xxA-S47.2xxD,S47.9xxA-S47.9xxD, S57.xxx,S67.xxx, S77.xxx,S87.xxx,S97.xxx, T79.Axx only for posttraumatic crush injury of Gustilo type III B and C
- when paired with ICD-10--CM codes T66.xxxA only for osteoradionecrosis and soft tissue radiation injury
- when paired with ICD-10-CM codes T86.820-T86.829,T82.898A/T82.898D, T82.9xxA/T82.9xxD, T83.89xA/T83.89xD, T83.9xxA/T83.9xxD, T84.89xA/T84.89xD, T84.9xxA/T84.9xxD, T85.89xA/T85.89xD, T859xxA/T859xxD only for compromised myocutaneous flaps

Code	Code description	List/Line Placement
99415	Prolonged clinical staff service (the service beyond the typical service time) during an evaluation and management service in the office or outpatient setting, direct patient contact with physician supervision; first hour each additional 30 minutes	**E&M Lines**
99416	each additional 30 minutes (List separately in addition to code for prolonged service)	**E&M Lines**
10035	Placement of soft tissue localization device(s) (eg, clip, metallic pellet, wire/needle, radiative seeds), percutaneous, including imaging guidance; first lesion	**Diagnostic Procedures File**
10036	each additional lesion (List separately in addition to code for primary procedure)	**Diagnostic Procedures File**
31652	Bronchoscopy with endobrochial ultrasound (EBUS) guided transtracheal and/or transbrochial sampling (eg, aspiration[s]/biopsy([ies]), one or two mediastinal and/or hilar lymph node stations or structures	**Diagnostic Procedures File**
31653	Bronchoscopy with endobrochial ultrasound (EBUS) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy([ies]), 3 or more mediastinal and/or hilar lymph node stations or structures	**Diagnostic Procedures File**
31654	Bronchoscopy with transendoscopic endobronchial ultrasound (EBUS) during bronchoscopic diagnostic or therapeutic intervention(s) for peripheral lesion(s) (List separately in addition to code for primary procedure[s])	**Diagnostic Procedures File**
33477	Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed	**73** ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION **86** MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS **115** CONGENITAL HEART BLOCK; OTHER OBSTRUCTIVE ANOMALIES OF HEART **190** RHEUMATIC MULTIPLE VALVULAR DISEASE **193** CHRONIC ISCHEMIC HEART DISEASE **262** DISEASES OF MITRAL, TRICUSPID, AND PULMONARY VALVES **290** COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT

Code	Code description	List/Line Placement
37252	Intravascular ultrasound (noncoronary vessel) during diagnostic evaluation and/or therapeutic intervention, including radiological supervision and interpretation; initial noncoronary vessel	**Diagnostic Procedures File**
37253	each additional noncoronary vessel (List separately in addition to code for primary procedure)	**Diagnostic Procedures File**
39401	Mediastinoscopy; includes biopsy(ies) of mediastinal mass (eg, lymphoma), when performed	**Diagnostic Procedures File**
39402	with lymph node biopsy(ies) (eg, lung cancer staging)	**Diagnostic Procedures File**
43210	Esophagogastroduodenoscopy with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed	**60** ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE **385** ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS
47531	Injection procedure for cholangiography, percutaneous, complete diagnostic procedure including imaging guidance (eg, ultrasound and/or fluoroscope) and all associated radiological supervision and interpretation; existing access	**Diagnostic Procedures File**
47532	new access(eg, percutaneous transhepatic cholangiogram)	**Diagnostic Procedures File**
47533	Placement of biliary drainage catheter, percutaneous, including diagnostic cholangiography when performed, including diagnostic cholangiography when performed, imaging guidance (eg, ultrasound and/or fluoroscopy), and all associated radiological supervision and interpretation; external	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **84** INJURY TO INTERNAL ORGANS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY
47534	internal - external	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY

Code	Code description	List/Line Placement
47535	Conversion of external biliary drainage catheter to internal-external biliary drainage catheter, percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY
47536	Exchange of biliary drainage catheter (eg, external, internal-external, or conversion of internal-external to external only), percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **428** COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT **439** CANCER OF GALLBLADDER AND OTHER BILIARY
47537	Removal of biliary drainage catheter, percutaneous, requiring fluoroscopic guidance (eg, with concurrent indwelling biliary stents), including diagnostic cholangiography when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **84** INJURY TO INTERNAL ORGANS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **428** COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT **439** CANCER OF GALLBLADDER AND OTHER BILIARY
47538	Placement of stent(s) into bile duct, percutaneous, including diagnostic cholangiography, imaging guidance (eg, fluoroscopy and/or ultrasound), balloon dilation, catheter exchange(s) and catheter removal(s) when performed, and all associated radiological supervision and interpretation, each stent; existing access	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY

Code	Code description	List/Line Placement
47539	new access, without placement of separate biliary drainage catheter	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY
47540	new access, with placement of separate biliary drainage catheter (eg, external or internal - external)	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **439** CANCER OF GALLBLADDER AND OTHER BILIARY
47541	Placement of access through the biliary tree and into small bowel to assist with an endoscopic biliary procedure (eg, rendezvous procedure), percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, ultrasound and/or fluoroscopy), and all associated radiological supervision and interpretation, new access	**Diagnostic Procedures File**
47542	Balloon dilation of biliary duct(s) or of ampulla (sphincteroplasty), percutaneous, including imaging guidance (eg, Fluoroscopy), and all associated radiological supervision and interpretation, each duct (List separately in addition to code for primary procedure)	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **194** NEOPLASMS OF ISLETS OF LANGERHANS **199** ACUTE PANCREATITIS **255** CHRONIC PANCREATITIS **290** COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER **320** CANCER OF LIVER **321** CANCER OF PANCREAS **439** CANCER OF GALLBLADDER AND OTHER BILIARY **645** GALLSTONES WITHOUT CHOLECYSTITIS

Code	Code description	List/Line Placement
47543	Endoluminal biopsy(ies) of biliary tree, percutaneous, and method(s) (eg, brush, forceps, and/or needle), including imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation, single or multiple (List separately in addition to code for primary procedure)	**Diagnostic Procedures File**
47544	Removal of calculi/debris from biliary duct(s) and/or gallbladder, percutaneous, including destruction of calculi by method (eg, mechanical , electrohydraulic lithotripsy) when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation (List separately in addition to code for primary procedure)	**59** COMPLICATED STONES OF THE GALLBLADDER AND BILE DUCTS; CHOLECYSTITIS **105** CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM AND ABDOMINAL WALL EXCLUDING NECROSIS; CHRONIC INTESTINAL PSEUDO-OBSTRUCTION **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER
49185	Sclerotherapy of a fluid collection (eg, lymphocele, cyst, or seroma), percutaneous, including contrast injection(s) sclerosant injection(s), diagnostic study, imaging guidance (eg, ultrasound, fluoroscopy) and radiological supervision and interpretation when performed	**229** DISORDERS OF PARATHYROID GLAND; BENIGN NEOPLASM OF PARATHYROID GLAND; DISORDERS OF CALCIUM METABOLISM **298** ANOMALIES OF GALLBLADDER, BILE DUCTS, AND LIVER 427 LYMPHEDEMA **427** LYMPHEDEMA **428** COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT **484** BREAST CYSTS AND OTHER DISORDERS OF THE BREAST **547** HYDROCELE **559** CYST OF KIDNEY, ACQUIRED **569** PLEURISY **596** GANGLION **607** DISORDERS OF SOFT TISSUE **634** CYST, HEMORRHAGE, AND INFARCTION OF THYROID
50430	Injection procedure for antegrade nephrostogram and/or ureterogram, complete diagnostic procedure including imaging guidance (eg, ultrasound and fluoroscopy) and all associated radiological supervision and interpretation; new access	**Diagnostic Procedures File**
50431	existing access	**Diagnostic Procedures File**

Code	Code description	List/Line Placement
50432	Placement of nephrostomy catheter, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation	**184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **235** URINARY FISTULA **357** URINARY SYSTEM CALCULUS
50433	Placement of nephroureteral catheter, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation, new access	**184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **235** URINARY FISTULA **357** URINARY SYSTEM CALCULUS
50434	Convert nephrostomy catheter to nephroureteral catheter, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation, via pre-existing nephrostomy tract	**184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **235** URINARY FISTULA **357** URINARY SYSTEM CALCULUS
50435	Exchange nephrostomy catheter, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation	**184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **235** URINARY FISTULA **290** COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT **357** URINARY SYSTEM CALCULUS
50606	Endoluminal biopsy of ureter and/or renal pelvis, non-endoscopic, including imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation (List separately in addition to code for primary procedure)	**Diagnostic Procedures File**
50693	Placement of ureteral stent, percutaneous, including diagnostic nephrostogram and/or ureterogram when performed, imaging guidance (eg, ultrasound and/or fluoroscopy), and all associated radiological supervision and interpretation ; pre-existing nephrostomy tract	**51** DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS **53** CONGENITAL HYDRONEPHROSIS **84** INJURY TO INTERNAL ORGANS **184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **275** CANCER OF BLADDER AND URETER **357** URINARY SYSTEM CALCULUS

Code	Code description	List/Line Placement
50694	new access, without separate nephrostomy catheter	**51** DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS **53** CONGENITAL HYDRONEPHROSIS **84** INJURY TO INTERNAL ORGANS **184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **275** CANCER OF BLADDER AND URETER **357** URINARY SYSTEM CALCULUS
50695	new access with separate nephrostomy catheter	**51** DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS **53** CONGENITAL HYDRONEPHROSIS **84** INJURY TO INTERNAL ORGANS **184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **275** CANCER OF BLADDER AND URETER **357** URINARY SYSTEM CALCULUS
50705	Ureteral embolization or occlusion, including imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation (List separately in addition to code for primary procedure)	**Services Recommended for Non-Coverage Table**
50706	Balloon dilation, ureteral stricture, including imaging guidance (eg, ultrasound and/or fluoroscopy) and all associated radiological supervision and interpretation (List separately in addition to code for primary procedure)	**184** URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER **332** FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
54437	Repair of traumatic corporeal tear(s)	**212** DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT **332** FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
54438	Replantation, penis, complete amputation including urethral repair	**212** DEEP OPEN WOUND, WITH OR WITHOUT TENDON OR NERVE INVOLVEMENT **332** FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION

Code	Code description	List/Line Placement
61645	Percutaneous arterial transluminal mechanical thrombectomy and/or infusion for thrombolysis, intracranial , any method, including diagnostic angiography, fluoroscopic guidance, catheter placement, and intraprocedural pharmacological thrombolytic injection(s)	**Services Recommended for Non-Coverage Table**
61650	Endovascular intracranial prolonged administration of pharmacologic agent(s) other than for thrombolysis, arterial, including catheter placement diagnostic angiography, and imaging guidance, initial vascular territory	**Services Recommended for Non-Coverage Table**
61651	each additional vascular territory (List separately in addition to code for primary procedure)	**Services Recommended for Non-Coverage Table**
64461	Paravertebral block (PVB) (paraspinous block), thoracic; single injection site (includes imaging guidance, when performed)	**Ancillary List**
64462	second and any additional injection site(s) (includes imaging guidance, when performed) (List separately in addition to code for primary procedure)	**Ancillary List**
64463	continuous infusion by catheter (includes imaging guidance, when performed)	**Ancillary List**
65785	Implantation of intrastromal corneal ring segments	**Services Recommended for Non-Coverage Table**
69209	Removal impacted cerumen using irrigation/lavage, unilateral	**316** HEARING LOSS - AGE 5 OR UNDER 395 ACUTE OTITIS MEDIA **432** NON-MALIGNANT OTITIS EXTERNA **450** HEARING LOSS - OVER AGE OF FIVE **479** CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM **503** CERUMEN IMPACTION
72081	Radiologic examination, spine, entire thoracic and lumbar, including skull, cervical and sacral spine if performed (eg, scoliosis evaluation); one view	**Diagnostic Procedures File**
72082	2 or 3 views	**Diagnostic Procedures File**
72083	4 or 5 views	**Diagnostic Procedures File**
72084	minimum of 6 views	**Diagnostic Procedures File**

Code	Code description	List/Line Placement
73501	Radiologic examination, hip, unilateral, with pelvis when performed; 1 view	**Diagnostic Procedures File**
73502	2 - 3 views	**Diagnostic Procedures File**
73503	minimum of 4 views	**Diagnostic Procedures File**
73521	Radiologic examination, hips, bilateral, with pelvis when performed; 2 views	**Diagnostic Procedures File**
73522	3-4 views	**Diagnostic Procedures File**
73523	minimum of 5 views	**Diagnostic Procedures File**
73551	Radiologic examination, femur; 1 view	**Diagnostic Procedures File**
73552	minimum 2 views	**Diagnostic Procedures File**
74712	Magnetic resonance (eg, proton) imaging, fetal, including placental and maternal pelvic imaging when performed; single or first gestation	**1** PREGNANCY
74713	each additional gestation (List separately in addition to code for primary procedure)	**1** PREGNANCY
77767	Remote afterloading high dose rate radionuclide skin surface brachytherapy, includes basic dosimetry, when performed, lesion diameter up to 2.0 cm or 1 channel	**Services Recommended for Non-Coverage Table**
77768	Lesion diameter over 2.0 cm or 2 or more channels, or multiple lesions	**Services Recommended for Non-Coverage Table**

Code	Code description	List/Line Placement
77770	Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 1 channel	**130** BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD **137** CANCER OF CERVIX **161** CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS **195** CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER **204** CANCER OF SOFT TISSUE **213** CANCER OF UTERUS **263** CANCER OF PENIS AND OTHER MALE GENITAL ORGANS **266** CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY **267** CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS **275** CANCER OF BLADDER AND URETER **291** CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS **292** CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX **299** CANCER OF BRAIN AND NERVOUS SYSTEM **319** CANCER OF ESOPHAGUS **334** CANCER OF PROSTATE GLAND **377** BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS **595** SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS

Code	Code description	List/Line Placement
77771	2-12 channels	**130** BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD **137** CANCER OF CERVIX **161** CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS **195** CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER **204** CANCER OF SOFT TISSUE **213** CANCER OF UTERUS **263** CANCER OF PENIS AND OTHER MALE GENITAL ORGANS **266** CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY **267** CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS **275** CANCER OF BLADDER AND URETER **291** CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS **292** CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX **299** CANCER OF BRAIN AND NERVOUS SYSTEM **319** CANCER OF ESOPHAGUS **334** CANCER OF PROSTATE GLAND **377** BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS **595** SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS

Code	Code description	List/Line Placement
77772	over 12 channels	**130** BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD **137** CANCER OF CERVIX **161** CANCER OF COLON, RECTUM, SMALL INTESTINE AND ANUS **195** CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER **204** CANCER OF SOFT TISSUE **213** CANCER OF UTERUS **263** CANCER OF PENIS AND OTHER MALE GENITAL ORGANS **266** CANCER OF RETROPERITONEUM, PERITONEUM, OMENTUM AND MESENTERY **267** CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS **275** CANCER OF BLADDER AND URETER **291** CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS **292** CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX **299** CANCER OF BRAIN AND NERVOUS SYSTEM **319** CANCER OF ESOPHAGUS **334** CANCER OF PROSTATE GLAND **377** BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS **595** SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS
78265	Gastric emptying study with small bowel transit	**Services Recommended for Non-Coverage Table**
78266	Gastric emptying study with small bowel and colon transit, multiple days	**Services Recommended for Non-Coverage Table**

Code	Code description	List/Line Placement
80081	Obstetrics panel (includes HIV testing) This panel must include the following: Blood count , complete (CBC) and automated differential WBC count (85025 or 85027 and 85009) OR Blood count, complete (CBC) and automated (85027) and appropriate manual differential WBC count (85007 or 85009) Hepatitis B surface antigen (HBsAg) (87340) HIV-1 antigen(s) , with HIV-1 and HIV-2 antibodies, single result (87389) Antibody , rubella (86762) Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART) (86592) Antibody screen, RBC, each serum technique (86850) Blood typing, ABO (86900) AND Blood typing, Rh (D) (86901) (When syphilis screening is performed using a treponemal antibody approach [86780], do not use 80081. Use the individual codes for the tests performed in the Obstetric panel)	**1** PREGNANCY
81170	*ABL 1 (ABL proto-oncogene 1 , non-receptor tyrosine kinase)* (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain	**Diagnostic Procedures File**
81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis	**Diagnostic Procedures File**
81218	*CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha)* (eg, acute myeloid leukemia), gene analysis, full gene sequence	**Diagnostic Procedures File**
81219	*CALR (calreticulin)* (eg, myeloproliferative disorders), gene analysis, common variants in exon 9	**Services Recommended for Non-Coverage Table**
81272	*KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog)* (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18,)	**Diagnostic Procedures File**
81273	*KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog)* (eg, mastocytosis, gene analysis, D816 variant(s)	**Services Recommended for Non-Coverage Table**
81276	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis additional variants(s) (eg, codon 61, codon 146)	**Diagnostic Procedures File**

Code	Code description	List/Line Placement
81311	*NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog)* (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)	**Services Recommended for Non-Coverage Table**
81314	*PDGFRA (platelet-derived growth factor receptor, alpha polypeptide)* (eg, gastrointestinal stromal tumor [GIST],gene analysis, targeted sequence analysis (eg, exons 12, 18)	**Diagnostic Procedures File**
81412	*Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA IKBKAP, MCOLN1 and SMPD1*	**Diagnostic Procedures File**
81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); geonomic sequence analysis panel, must include sequencing of at least 14 genes, including *ATM, BRCA1, BRCA2,BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11 AND TP53*	**Services Recommended for Non-Coverage Table**
81433	duplication/deletion analysis panel, must include analyses for *BRCA1, BRCA2, MLH1, MSH2, AND STK11*	**Services Recommended for Non-Coverage Table**
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophyl, genomic sequence analysis panel, must include sequencing of at least 15 genes, including *ABCA4, CNGA1, CRB1, EYS, PDE6A, PRPF31, PRPH2, RDH12, RHO, RP1 RP2, RPE65, RPGR,* and *USH2A*	**Diagnostic Procedures File**
81437	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma; genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127. and VHL	**Diagnostic Procedures File**
81438	duplication/deletion *analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL*	**Diagnostic Procedures File**

Code	Code description	List/Line Placement
81442	Noonan spectrum disorders (eg, Noonan Syndrome, cardio -facio - cutaneous syndrome, Costello syndrome, LEOPARD Syndrome, Noonan-like syndrome), genomic sequence analysis panel , must include sequencing of at least 12 genes, including *BRAF, CBL, HRAS, DRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1,SHOC2, and SOS1*	**Diagnostic Procedures File**
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score	**Services Recommended for Non-Coverage Table**
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PRC of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score	**Services Recommended for Non-Coverage Table**
81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score	**Services Recommended for Non-Coverage Table**
81528	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (*KRAS* mutations, promoter methylation of *NDRG4* and *BMP3)* and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result	**Services Recommended for Non-Coverage Table**
81535	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination	**Services Recommended for Non-Coverage Table**
81536	each additional single drug or drug combination (List separately in addition to code for primary procedure)	**Services Recommended for Non-Coverage Table**
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm, reported as good versus poor overall survival	**Services Recommended for Non-Coverage Table**

Code	Code description	List/Line Placement
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue , algorithm reported as a probability of a predicted main cancer type and subtype	**Services Recommended for Non-Coverage Table**
81545	Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)	**Services Recommended for Non-Coverage Table**
81595	Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as rejection risk score	**245** CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION **268** CONGESTIVE HEART FAILURE, CARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE
88350	Immunofluroescence, per specimen, each additional single antibody stain procedure (List separately in addition to code for primary procedure)	**Diagnostic Procedures File**
90625	Cholera vaccine, live adult dosage, 1 dose schedule, for oral use	**Services Recommended for Non-Coverage Table**
90620	Meningococcal recombinant protein and outer membrane vesicle vaccine, serogroup B (MenB), 2 dose schedule for intramuscular use	**3** PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
90621	Meningococcal recombinant lipoprotein vaccine, serogroup B (MenB), 3 dose schedule, for intramuscular use	**3** PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
92537	Caloric vestibular test with recording, bilateral; bithermal (ie, one warm and one cool irrigation in each ear for a total of four irrigations)	**297** NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS **422** MENIERE'S DISEASE **515** VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM
92538	monothermal (ie, one irrigation in each ear for a total of two irrigations)	**297** NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS **422** MENIERE'S DISEASE **515** VERTIGINOUS SYNDROMES AND OTHER DISORDERS OF VESTIBULAR SYSTEM

Code	Code description	List/Line Placement
93050	Arterial pressure waveform analysis for assessment of central arterial pressures, includes obtaining waveform(s), digitization and application of nonlinear mathematical transformations to determine central arterial pressures and augmentation index, with interpretation and report, upper extremity artery, non-invasive	**Services Recommended for Non-Coverage Table**
96931	Reflection confocal microscopy (RCM) for cellular and sub-cellular imaging of skin ; image acquisition and interpretation and report, , first lesion	**Services Recommended for Non-Coverage Table**
96932	image acquisition only, first lesion	**Services Recommended for Non-Coverage Table**
96933	interpretation and report only, first lesion	**Services Recommended for Non-Coverage Table**
96934	image acquisition and interpretation and report, each additional lesion (List separately in addition to code for primary procedure)	**Services Recommended for Non-Coverage Table**
96935	image acquisition only, each additional lesion (List separately in addition to code for primary procedure)	**Services Recommended for Non-Coverage Table**
99177	Instrument based ocular screening (eg, photoscreening, automated-fractions),bilateral; with onsite analysis	**Services Recommended for Non-Coverage Table**

HCPCS CODES

G0296	Counseling visit to discuss need for lung cancer screening (ldct) using low dose ct scan (service is for eligibility determination and shared decision making)	**3** PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
G0297	Low dose ct scan (ldct) for lung cancer screening	**3** PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
G0298	Hiv antigen/antibody, combination assay, screening	**Services Recommended for Non-Coverage Table**
G0475	Hiv antigen/antibody, combination assay, screening	**Services Recommended for Non-Coverage Table**

Appendix C
New Guidelines

GUIDELINE NOTE XXX, SCLEROTHERAPY OF FLUID COLLECTIONS

Lines 172, 229, 298, 427, 428, 484, 547, 559, 569, 596, 607, 634

Sclerotherapy for fluid collections (CPT 49185) is included on these lines only for the treatment of cysts, seromas or lymphoceles which are causing bleeding, infection, severe pain, organ torsion, or organ dysfunction.

GUIDELINE NOTE XXX, FETAL MRI

Line 1

Fetal MRI (CPT 74712-74713) is included on this line only when all of the following conditions are met:

1) Abnormalities are found on fetal ultrasound performed by an experienced sonologist which cannot be adequately further evaluated by 2D or 3D ultrasound
2) The information obtained by fetal MRI is necessary for decisions about fetal or neonatal therapy, delivery planning, or to advise a family about prognosis
3) The fetus is 18 weeks gestational age or older
4) The MRI is performed and interpreted at a center with technicians and radiologists who are either trained or highly experienced in fetal MRI and which has appropriate MRI equipment, with a minimum of a 1.5 Tesla magnet

GUIDELINE NOTE XXX, CARDIAC TRANSPLANT GENETIC TESTING FOR TRANSPLANT REJECTION

Lines 245,268

Genetic testing for cardiac transplant rejection (CPT 81595) is included on these lines only for patients at least 1 year post transplant who are without clinical signs of rejection.

GUIDELINE NOTE XXX, UNSPECIFIED CONDUCT DISORDER

Lines 425, 483

ICD-10 F91.9 (Conduct disorder, unspecified) is included on line 425 only for children ages 5 and younger who cannot be diagnosed with a more specific mental health diagnosis. This diagnosis is included on line 483 for older children and adolescents.

GUIDELINE NOTE XXX, BUERGER'S DISEASE

Lines 240, 657

Buerger's disease (ICD-10 I73.1) is included on line 240 only when ulceration or gangrene is present. Otherwise, this diagnosis is included on line 657. TI73.1 does not pair on line 240 with revascularization procedures, bypass graft procedures, or angioplasty.

Appendix C
New Guidelines

Guideline Note XXX, PLANNED OUT-OF-HOSPITAL BIRTH

Lines 1, 2

Planned out-of-hospital birth is included on these lines when appropriate risk assessments are performed, and the consultation and transfer criteria are followed, and no high risk coverage exclusion criteria exist. Risk assessment should be done initially when planning the location of birth, and updated throughout pregnancy, labor, and delivery to determine if out-of-hospital birth is still appropriate.

The clinical and/or diagnostic assessment of each criterion, with the exception of those marked with an asterisk, is necessary for planned out-of-hospital birth to be included on these lines. (Criteria marked with an asterisks may not be known or not be pertinent if there is no clinical indication for concern and additional diagnostic testing is not indicated.)

An ultrasound is required to rule out certain risk criteria (e.g. multiple gestation, placenta previa, and life threatening congenital anomalies). Certain risk criteria require serial measurements such as fundal height and blood pressure.

If a woman refuses a required clinical or diagnostic assessment, then ascertainment of her risk status is unknowable and she does not meet criteria for coverage for an out-of-hospital birth.

Documentation of continuing appropriate risk assessment and routine prenatal care is required.

High-risk coverage exclusion criteria:

Complications in a previous pregnancy:

Maternal surgical history

- Cesarean section or other hysterotomy
- Uterine rupture
- Retained placenta requiring surgical removal
- Fourth-degree laceration without satisfactory functional recovery

Maternal medical history

- Pre-eclampsia requiring preterm birth
- Eclampsia
- HELLP syndrome

Fetal and placental

- Unexplained stillbirth/neonatal death or previous death related to intrapartum difficulty
- Baby with neonatal encephalopathy
- Placental abruption with adverse outcome

Appendix C
New Guidelines

Complications of current pregnancy:

Maternal

- Induction of labor
- Prelabor rupture of membranes > 24 hours
- Pre-existing chronic hypertension; Pregnancy-induced hypertension with diastolic blood pressure greater than or equal to 90 mmHg or systolic blood pressure greater than or equal to 140 mmHg on two consecutive readings taken at least 30 minutes apart
- Unknown group B strep carrier state
- Lack of informed consent on group B strep prophylaxis, if mother is Group B strep positive.
- Eclampsia or pre-eclampsia
- Anemia – hemoglobin less than 8.5 g/dL
- Thrombocytopenia (platelets <100,000)
- Thrombosis/thromboembolism or other maternal bleeding disorder*
- Maternal mental illness requiring inpatient care*
- Drug or alcohol use with high risk for adverse effects to fetal or maternal health
- Unknown, or positive, syphilis, HIV, or Hepatitis B status
- Current active infection of varicella at the time of labor; rubella infection anytime during pregnancy; active infection (outbreak) of genital herpes at the time of labor*
- Refractory hyperemesis gravidarum*
- Diabetes, type I or II, uncontrolled gestational diabetes, or gestational diabetes controlled with medication

Placental

- Low lying placenta within 2 cm or less of cervical os at term; placenta previa, vasa previa
- Placental abruption/abnormal bleeding
- Recurrent antepartum hemorrhage
- Uteroplacental insufficiency*

Fetal

- Gestational age - preterm or postdates (defined as gestational age < 37 weeks + 0 days or > 41 weeks + 6 days)
- Multiple gestation
- Non-cephalic fetal presentation
- IUGR (defined as fetal weight less than fifth percentile using ethnically-appropriate growth tables, or concerning reduced growth velocity on ultrasound)*
- Oligohydramnios or polyhydramnios*
- Abnormal fetal heart rate/Doppler/surveillance studies
- Blood group incompatibility with atypical antibodies, or Rh sensitization
- Molar pregnancy

Appendix C
New Guidelines

Transfer criteria:

If out-of-hospital birth is planned, certain intrapartum and postpartum complications may necessitate transfer to a hospital to meet coverage criteria. For these indications, an attempt should be made to transfer the mother and/or her newborn; however, imminent fetal delivery may delay or preclude actual transfer prior to birth.

Maternal

- Temperature ≥ 38.0 C
- Maternal infection requiring hospital treatment (e.g. endometritis or wound infection)
- Hemorrhage (hypovolemia, shock, need for transfusion)
- Retained placenta > 60 minutes
- Laceration requiring hospital repair (e.g., extensive vaginal, cervical or third- or fourth-degree trauma)
- Enlarging hematoma
- Bladder or rectal dysfunction

Fetal and uterine

- Repetitive or persistent abnormal fetal heart rate pattern
- Thick meconium staining of amniotic fluid
- Prolapsed umbilical cord
- Failure to progress (as defined by the American Congress of Obstetricians and Gynecologists, March 2014, found at http://www.acog.org/Resources-And-Publications/Obstetric-Care-Consensus-Series/Safe-Prevention-of-the-Primary-Cesarean-Delivery)/failure of head to engage in active labor
- Chorioamnionitis or other serious infection (including toxoplasmosis, rubella, CMV, HIV, etc.)
- Uterine rupture, inversion or prolapse

If the infant is delivered out-of-hospital, the following complications require transfer to a hospital for the out-of-hospital birth to meet coverage criteria:

- Low Apgar score (< 5 at 5 minutes, < 7 at 10 minutes)
- Weight less than 5th percentile for gestational age
- Unexpected significant or life-threatening congenital anomalies
- Respiratory or cardiac irregularities, cyanosis, pallor
- Temperature instability, fever, suspected infection or dehydration
- Hyperglycemia/hypoglycemia unresponsive to treatment
- Hypotonia, tremors, seizures, hyperirritability
- Excessive bruising, enlarging cephalohematoma, significant birth trauma
- Vomiting/diarrhea

Appendix C
New Guidelines

Consultation criteria:

Certain high risk conditions require consultation (by a provider of maternity care who is credentialed to admit and manage pregnancies in a hospital) for coverage of a planned out-of-hospital birth to be recommended. These complications include (but are not limited to) patients with:

Complications in a previous pregnancy:

Maternal

- More than three first trimester spontaneous abortions, or more than one second trimester spontaneous abortion
- More than one preterm birth, or preterm birth less than 34 weeks 0 days in most recent pregnancy
- Pre-eclampsia, not requiring preterm birth
- Cervical insufficiency/prior cerclage
- Third degree laceration; fourth-degree laceration with satisfactory functional recovery
- Life-threatening congenital anomalies (unless fatal anomalies with nonresuscitation planned)
- Postpartum hemorrhage requiring additional pharmacologic treatment or blood transfusion
- Retained placenta requiring manual removal

Fetal

- Child with congenital and/or hereditary disorder
- Baby > 4.5 kg or 9 lbs 14 oz
- Shoulder dystocia, with or without fetal clavicular fracture
- Unexplained stillbirth/neonatal death or previous death unrelated to intrapartum difficulty
- Unresolved intrauterine growth restriction (IUGR) or small for gestational age (defined as fetal or birth weight less than fifth percentile using ethnically-appropriate growth tables)
- Blood group incompatibility, and/or Rh sensitization

Complications of current pregnancy:

Maternal

- Inadequate prenatal care (defined as less than five prenatal visits or care began in the third trimester)
- Body mass index at first prenatal visit of greater than 35 kg/m^2
- History of maternal seizure disorder (excluding eclampsia)
- Gestational diabetes, diet-controlled
- Maternal mental illness with suspicion for psychosis or potential harm to self or infant under outpatient psychiatric care
- Maternal anemia with hemoglobin < 10.5 g/dL, unresponsive to treatment
- Third-degree laceration not requiring hospital repair
- Laparotomy during pregnancy

Fetal

- Fetal macrosomia (estimated weight >4.5 kg or 9 lbs 14 oz)
- Confirmed intrauterine death
- Family history of genetic/heritable disorders that would impact labor, delivery or newborn care

Appendix D

New Multisector Interventions

MULTISECTOR INTERVENTIONS: TOBACCO PREVENTION AND CESSATION

Benefit coverage for smoking cessation on Line 5 and in GUIDELINE NOTE 4, *TOBACCO DEPENDENCE* is intended to be offered with minimal barriers, in order to encourage utilization. To further prevent tobacco use and help people quit, additional evidence-based policy and programmatic interventions from a population perspective are available here:

- Oregon Public Health Division's Health Promotion and Chronic Disease Prevention Section: Evidence-Based Strategies for Reducing Tobacco Use A Guide for CCOs https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Documents/evidence-based_strategies_reduce_tob_use_guide_cco.pdf
- Community Preventive Services Task Force (supported by the CDC) - What Works: Tobacco Use http://www.thecommunityguide.org/about/What-Works-Tobacco-factsheet-and-insert.pdf

The Community Preventive Services Task Force identified the following evidence-based strategies:

Appendix D
New Multisector Interventions

TASK FORCE FINDINGS ON TOBACCO USE

The Community Preventive Services Task Force (Task Force) has released the following findings on what works in public health to prevent tobacco use. These findings are compiled in The Guide to Community Preventive Services (The Community Guide) and listed in the table below. Use the findings to identify strategies and interventions you could use for your community.

Legend for Task Force Findings: Recommended | Insufficient Evidence | Recommended Against (See reverse for detailed descriptions.)

Intervention	Task Force Finding
Reducing Tobacco Use Initiation	
Increasing the unit price of tobacco products	Recommended
Mass media campaigns when combined with other interventions	Recommended
Smoke-free policies	Recommended
Increasing Tobacco Use Cessation	
Increasing the unit price of tobacco products	Recommended
Mass media campaigns when combined with other interventions	Recommended
Mass-reach health communication interventions	Recommended
Mobile phone-based interventions	Recommended
Multicomponent interventions that include client telephone support	Recommended
Smoke-free policies	Recommended
Provider reminders when used alone	Recommended
Provider reminders with provider education	Recommended
Reducing client out-of-pocket costs for cessation therapies	Recommended
Internet-based interventions	Insufficient Evidence
Mass media – cessation contests	Insufficient Evidence
Mass media – cessation series	Insufficient Evidence
Provider assessment and feedback	Insufficient Evidence
Provider education when used alone	Insufficient Evidence

Intervention	Task Force Finding
Reducing Exposure to Environmental Tobacco Smoke	
Smoke-free policies	Recommended
Community education to reduce exposure in the home	Insufficient Evidence
Restricting Minors' Access to Tobacco Products	
Community mobilization with additional interventions	Recommended
Sales laws directed at retailers when used alone	Insufficient Evidence
Active enforcement of sales laws directed at retailers when used alone	Insufficient Evidence
Community education about youth's access to tobacco products when used alone	Insufficient Evidence
Retailer education with reinforcement and information on health consequences when used alone	Insufficient Evidence
Retailer education without reinforcement when used alone	Insufficient Evidence
Laws directed at minors' purchase, possession, or use of tobacco products when used alone	Insufficient Evidence
Decreasing Tobacco Use Among Workers	
Smoke-free policies	Recommended
Incentives and competitions to increase smoking cessation combined with additional interventions	Recommended
Incentives and competitions to increase smoking cessation when used alone	Insufficient Evidence

Visit the "Tobacco Use" page of The Community Guide website at www.thecommunityguide.org/tobacco to find summaries of Task Force findings and recommendations on tobacco use. Click on each topic area to find results from the systematic reviews, included studies, evidence gaps, and journal publications.

The Centers for Disease Control and Prevention provides administrative, research, and technical support for the Community Preventive Services Task Force.

MINUTES

Evidence-based Guidelines Subcommittee

Clackamas Community College
Wilsonville Training Center, Rooms 111-112
29353 SW Town Center Loop E
Wilsonville, Oregon 97070
November 5, 2015
2:00-5:00pm

Members Present: Wiley Chan, MD, Chair; Eric Stecker, MD, MPH (arrived at 2:05), Vice-Chair; Vern Saboe, DC; Beth Westbrook, PsyD; George Waldmann, MD; Alison Little, MD, MPH.

Members Absent: Bob Joondeph, JD

Staff Present: Darren Coffman; Catherine Livingston, MD, MPH; Jason Gingerich.

Also Attending: Adam Obley, MD, Craig Mosbaek (Center for Evidence-Based Policy), CJ Dantinne (OSIRIS), Dirk Sutherland (Alliqua Biomedical), Carol Howe and Lisa Chickadonz (American College of Nurse-Midwives), Jessie Little (OHA Actuarial Services), Erica Pettigrew (OHSU).

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1. CALL TO ORDER

Wiley Chan called the meeting of the Evidence-based Guidelines Subcommittee (EbGS) to order at 2:00 pm.

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2. MINUTES REVIEW

Chan asked that the September minutes be corrected to show approval of the scope document on Neuroimaging for Headache.

Minutes approved as amended 5-0 (Absent: Stecker).

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3. STAFF REPORT

Coffman welcomed Alison Little to the subcommittee, and announced that Vern Saboe will be rotating off of EbGS and onto VbBS when his HERC term ends at the end of the year. A new complimentary and alternative medicine representative is being sought for HERC, and when that person is appointed, they will join EbGS as well.

Coffman also suggested moving the November EbGS meeting to the first week of December in 2016. Waldmann said that date might be a problem for him. No decision was made.

Coffman also reported that HERC decided to open public meetings in listen-only mode. Members of the public will be allowed to call in, but only invited speakers will receive a code to allow them to be heard.

Livingston gave an update on the Coverage Guidance on Planned Out-of-Hospital Birth. It was discussed at the October VbBS and HERC meetings but discussion will be continued in November, when it will likely be approved. Livingston said some more minor changes were being suggested, including requiring documenting the absence of certain risk factors, which would end up meaning HIV, syphilis and hepatitis B would require screening in addition to other risk factors. There are many implementation considerations for this coverage guidance; she asked for feedback on how the subcommittee felt about the level of detail they got to in the coverage guidance.

Waldmann said that lack of malpractice insurance is one of the considerations for CCOs; for that reason he confirmed that coverage of the birth itself for providers lacking liability insurance would be provided by fee-for-service Medicaid and the mother and child would return to CCO coverage after the labor and delivery. He expressed concern that OHA fee-for-service staff might not do as much precertification work as the CCOs, but Livingston said there is a nurse responsible for reviewing these cases.

Westbrook responded to Livingston's question, saying that it was a detailed discussion for out-of-hospital birth, but she was willing to go into details if needed. Chan said that the Value-based Benefits Subcommittee is more accustomed to dealing with such implementation details, but the EbGS seems to be getting into that territory more and more. Westbrook said she is comfortable doing that to the extent that the group is reviewing the evidence rather than speculating. Livingston noted that the skin substitutes coverage guidance will get into some policy speculation issues.

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4. Review of public comment— Nitrous Oxide Use for Labor Pain Management

Robyn Liu reviewed the single public comment, which focused on safety issues. The response is that the guidance assumes that the gas will be used by qualified personnel and used in a safe way. No changes were made to the draft coverage guidance.

Livinston reviewed some clarifying edits made by staff during the public comment period, shown in track changes in the meeting packet. There was no discussion of these edits.

Stecker asked about the billing codes. There is an anesthesia code for nitrous oxide but it can only be used by anesthesiologists and nurse anesthetists. In a hospital setting, nitrous oxide would be billed as part of a bundled payment. In the out-of-hospital settings, implementers will need to find a way to reimburse this service.

Livingston invited public comment. Carol House offered public comment. She recently retired as program director for the midwifery center at OHSU. She asked about the use of nitrous oxide during the delivery of the placenta. Liu clarified that the delivery of placenta is the third stage of labor, so would be included with the existing language.

Motion to approve the draft coverage guidance for review by VbBS and HERC was approved 6-0.

DRAFT COVERAGE GUIDANCE

Nitrous oxide for labor pain is recommended for coverage (weak recommendation).

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5. Review need for updates on coverage guidances approved in 2013

For Induction of Labor, Liu reviewed the rescanning document. Livingston recommended not reviewing the topic as no change would be likely. After minimal discussion, the subcommittee voted 6-0 to defer consideration of a new coverage guidance for this topic until the next two-year review cycle.

For Recurrent Acute Otitis Media, Liu said this would likely be the most controversial. At the time that the coverage guidance was approved the American Academy of Pediatrics recommended use of prophylactic antibiotics. Liu said that there are new evidence reviews but they are poor quality and contradictory. The AAP no longer recommends use of prophylactic antibiotics, due in part to concerns about antibiotic resistance and limited benefit. Livingston said the staff recommendation is to review the topic again to address the AAP guideline as well as concerns about antibiotic resistance and adenoidectomies and tympanostomy tubes. After minimal discussion, the subcommittee voted 6-0 to recommend the development of a new coverage guidance on the topic.

For Neuroimaging for Headache, Livingston recommended not updating the coverage guidance until the next two-year cycle. After minimal discussion, the subcommittee voted 6-0 to defer consideration of a new coverage guidance for this topic until the next two-year review cycle.

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6. Review draft coverage guidance—Skin substitutes for chronic skin ulcers

Coffman introduced Dr. Foy White-Chu, who will serve as clinical expert for this topic. Dr. White-Chu is Associate Geriatric Fellowship Director at the Portland VA Medical Center. She is certified as a Physician Specialist in Wound Care by the Council for Medicine Education and Testing, and a Diplomate of the American Board of Internal Medicine, with Geriatric Medicine Subspecialty. For conflicts of interest, in addition to her employment, she provides clinical medical education training on wound care at regional conferences several times each year.

Liu reviewed the draft coverage guidance. Subcommittee members asked several questions about the regulatory context. Some of these products are FDA-approved and as such have approved indications for use. Others are said to qualify as human tissue products, which do not require such approval and thus are regulated differently for safe handling rather than clinical effectiveness. There is litigation over which products fall into which category. Livingston said initially that staff wanted to separate products by tissue type but discovered that this doesn't provide a useful distinction as the effectiveness of each product needs to be considered individually to determine efficacy.

When Liu reviewed the parameters for the literature search, Livingston mentioned that the original scope included only comparison to usual care, but the search also returned some head-to-head comparisons of different products. Stecker noted that there are problematic issues combining

comparisons to usual care and comparisons of multiple products. Livingston agreed and said that the subcommittee will discuss these where appropriate.

Liu also discussed that some industry stakeholders submitted studies that weren't found in staff's literature search because the articles were very recent or hadn't been indexed by MedLine. According to the Coverage Guidance methodology, these studies were not considered in the initial draft coverage guidance, but will be included if submitted as a part of public comments and reviewed along with other public comments. Staff has already notified stakeholders that they will need to resubmit the studies during the formal comment period. The search strategy included only systematic reviews, evidence-based guidelines meta-analyses and randomized controlled trials indexed in MedLine.

Before Liu reviewed the evidence around the eight products for which staff found evidence, Livingston explained that the staff recommendations were based on a requirement for at least low quality evidence of benefit to justify a coverage recommendation. No evidence that met inclusion criteria was found for the treatment of pressure ulcers, and evidence for many of the products was rated as very low quality, so coverage was not recommended for these. Staff also clarified the difference between the level of certainty about the outcome from what the outcome is. In some cases we have low certainty of benefit. This means that the evidence is weak and indicates that the product doesn't have a benefit for the selected outcome.

Livingston reviewed the cost issues. Some products are applied only once; others are applied multiple times with different maximum amounts for different products. She explained how the cost varies by setting of care and billing methodology for Medicare. Many of the costs are similar, but there are some outliers. Stecker questioned the usefulness of this analysis because of the higher variability. An insurer could instead approve spending for a particular dollar amount over a time period. Chan said that another approach would be to determine whether the benefit is cost effective. You would only compare costs if you had evidence of benefit for two products with different costs in the same application.

After Livingston and Liu reviewed the cost information, Stecker questioned the use of this level of detailed cost information. White-Chu explained that Apligraf is a perishable product sold in large sizes. Frequently much of the product is wasted because the wound is small, and she has had cases where the product was wasted because of shipping delays due to storms in the Midwest. Other products such as Epifix are sold in smaller sizes and have a long shelf life. Pricing evolves rapidly and depends on facility negotiations. Stecker expressed concern about going into this level of detail. For instance, with ablation for atrial fibrillation, payers don't specify the kinds of catheters a surgeon uses or what kinds of anesthesia or imaging he uses; using cost data in this way would go beyond the HERC coverage guidance on that topic. Westbrook said it may be worth these amounts to prevent an amputation; there needs to be room for clinicians to make decisions, including cost effectiveness decisions, for their patients.

Livingston then reviewed the Coverage Guidance box recommendation. Based on Liu's recommendation, Livingston endorsed changing the recommendation in the meeting materials for Oasis, changing it to a weak recommendation for coverage for diabetic foot ulcers based on the outcome of time to complete wound healing.

After discussion, the subcommittee decided to strike the paragraph on reference pricing and bundling, to leave such decisions to payers. In addition, the subcommittee revised the criteria for coverage of the products recommended for coverage. It moved requirements for offloading, multilayer compression dressings and tobacco cessation and made them part of the definition of prior appropriate wound care.

After discussion, the requirement for tobacco cessation was also changed to a requirement for participation in smoking cessation counseling. (The subcommittee didn't find sufficient evidence in this review to require smoking cessation, but did retain the requirement for provision of smoking cessation counseling.)

The subcommittee also added a requirement for an ABI (Ankle-Brachial Index) of 0.7 as evidence of adequate arterial blood flow.

The subcommittee added a definition of failure of conservative wound care as failing to achieve a 50 percent reduction in ulcer surface area. In place of the limit on additional use of products which had failed previously, the subcommittee added a clause requiring continued significant improvement at six week intervals for continued coverage. After extensive discussion, the subcommittee specifically decided not to add a maximum total duration for therapy or maximum number of applications for a particular product because of lack of evidence to support such a restriction. Coffman said that VbBS may consider putting an upper limit based on limited resources.

Livingston invited public comment.

CJ Dantinne testified representing Osiris, manufacturer of Grafix. He addressed the exclusion criteria for the Lavery study discussed earlier, which was HBa1c >12, or ABI >1.3 or <0.7. He said Noridian recently changed its criteria from requiring smoking cessation to requiring patients to be advised to stop smoking. He described the Grafix products, and cited the NICE guidance which finds benefits from Grafix based on a randomized trial which was stopped early for overwhelming efficacy. He said 34 million Medicaid lives have access to Grafix right now. In addition Noridian recently removed Grafix from the noncovered list.

Livingston said that staff would review the recommendation on Grafix based on this study during the public comment period. Liu said that this study had been included but the quality had been downgraded to very low based on lack of description of randomization and concealment as well as potential funder bias. No changes were made to the coverage guidance based on this testimony.

The subcommittee also discussed the strength of recommendation for Apligraf. After discussion the subcommittee decided to leave the recommendation as weak.

Motion to post the draft coverage guidance for public comment as amended was approved 6-0.

Staff note: After the meeting it was discovered that this part of Liu's presentation contained an error with respect to the OASIS Wound Matrix, so this change was removed from the version posted for comment. EbGS will discuss this matter along with the public comments.

DRAFT HERC Coverage Guidance

Skin substitutes for chronic venous leg ulcers and chronic diabetic foot ulcers are recommended for coverage *(weak recommendation)* when all of the following criteria are met:

1. Product is recommended for the type of ulcer being treated (see table below)
2. FDA indications and contraindications are followed, if applicable

3. Wound has adequate arterial flow (ABI > 0.7), no ongoing infection and a moist wound healing environment
4. For patients with diabetes, Hba1c level is < 12.
5. Prior appropriate wound care therapy (including but not limited to appropriate offloading, multilayer compression dressings and smoking cessation counseling) has failed to result in significant improvement (defined as at least a 50 percent reduction in ulcer surface area) of the wound over at least 30 days
6. Ulcer improves significantly over 6 weeks of treatment with skin substitutes, , with continued significant improvement every 6 weeks required for coverage of ongoing applications
7. Patients is able to adhere to the treatment plan

The following products are recommended/not recommended for coverage as shown below. All recommendations are weak recommendations except as specified.

Product	Diabetic foot ulcers	Venous leg ulcers
Dermagraft	Recommended	Not recommended
Apligraf	Recommended	Recommended
OASIS Wound Matrix	Not Recommended	Recommended
Epifix	Not recommended	Not recommended
Grafix	Not recommended	Not recommended
Graftjacket	Not recommended	Not recommended
Talymed	Not recommended	Not recommended
Theraskin	Not recommended	Not recommended
Other skin substitutes	Not recommended	Not recommended

The use of skin substitutes is not recommended for coverage of chronic skin ulcers other than venous leg ulcers and diabetic foot ulcers (e.g. pressure ulcers) *(weak recommendation).*

7. ADJOURNMENT

The meeting was adjourned at 4:32 pm. The next meeting is scheduled for February 4, 2016 from 2:00-5:00pm in Room 111-112 of the Wilsonville Training Center.

MINUTES

Health Technology Assessment Subcommittee

Clackamas Community College
Wilsonville Training Center, Room 210
29353 SW Town Center Loop E
Wilsonville, Oregon 97070
December 10, 2015
1:00-4:00pm

Members Present: Som Saha, MD, MPH (Chair Pro Tempore); Chris Labhart; Gerald Ahmann, MD; Leda Garside, RN, MBA; Mark Bradshaw, MD; Jim MacKay, MD (left at 3:40). Derrick Sorweide, DO (arrived 2:05)

Members Absent: Tim Keenen, MD

Staff Present: Darren Coffman; Cat Livingston, MD, MPH; Jason Gingerich.

Also Attending: Adam Obley, MD, Val King MD, MPH & Craig Mosbaek (OHSU Center for Evidence-based Policy), Amber Stifter (Medtronic), Joe Badolato, DO (FamilyCare), Valerie Halpin, MD (Legacy), Bruce Wolfe, MD (OHSU), Rene Taylor (DexCom).

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1. CALL TO ORDER

Saha called the meeting to order at 1 p.m.

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2. MINUTES REVIEW

Minutes from the September, 2015 meeting were reviewed and approved 6-0.

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3. STAFF REPORT

Coffman noted that the topic of Vertebroplasty, Sacroplasty and Kyphoplasty was inadvertently omitted from the public notice for this meeting. The rescan of this topic will come to a future meeting.

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4. REVIEW NEED FOR UPDATES ON COVERAGE GUIDANCES APPROVED IN 2013

Obley reviewed the results of the rescan for Continuous Glucose Monitoring provided in the meeting packet. Livingston said she recommends an update as there are randomized trials with mixed evidence. There are also implementation concerns about the duration and indications for these devices. Som said in a rescan, we'd only want to take up a topic if the evidence is likely to change the recommendation. Obley said there are two reasons to consider an update. First, the new randomized trial is the largest

and best-conducted to date. In addition, these devices are now being paired with insulin pumps, which is a novel use of the device.

Saha invited public comment.

Joe Badolato from FamilyCare testified that the evidence is mixed for this very expensive device. It is difficult to know when to start, when to stop use and for how long to continue use. He gave the example of a newly-diagnosed 8-year-old Type 1 diabetes patient who would qualify under the HERC guideline, but her HbA1c was barely over the limit after a short course of management without the device. Families are demanding the device and hoping for better control, but the evidence of significant benefit is lacking. In addition, the requirement for considering insulin pump therapy causes difficulty as the continuous monitors are usually prescribed before therapy. He said that these devices are being pushed by Byram and Medtronic representatives. He expressed surprise that HERC approved the current guideline based on limited evidence. In addition he said that determining compliance with previous treatment is difficult, as compliance isn't defined. He requested additional clarity from the next review.

Rene Taylor, a diabetes educator with DexCom, a manufacturer, also testified, requesting additional clarity around the requirement related to insulin pumps being considered or utilized. Consideration is not often documented in progress notes, and this is limiting access. There are devices approved for children as young as two years old, which are shown to reduce hypoglycemia in this vulnerable population. In addition, the evidence shows equivalence for the device with insulin injections or an insulin pump so the requirement for an insulin pump is not consistent with the evidence.

Staff noted an edit to the previously approved scope statement, adding mention that diabetes-related hospitalizations and emergency department visits were excluded as outcomes.

After brief additional discussion, the subcommittee voted 6-0 (Sorweide absent) to recommend the development of a new coverage guidance on the topic.

For Self Monitoring of Blood Glucose, Obley reviewed the rescanning summary. The reviews all suggested small improvements in HbA1c, but evidence is lacking on direct outcomes. Livingston said she doesn't believe this evidence has the potential to change the existing coverage guidance. The subcommittee voted 6-0 (Sorweide absent) to defer consideration of a new coverage guidance for this topic until the next two-year review cycle.

Obley reviewed the rescan for MRI for Breast Cancer. Livingston recommended not updating the current coverage guidance. The subcommittee voted 6-0 (Sorweide absent) to defer consideration of a new coverage guidance for this topic until the next two-year review cycle.

Obley reviewed the rescan for PET for Breast Cancer after initial diagnosis. Livingston recommended not updating the current coverage guidance. The subcommittee voted 6-0 (Sorweide absent) to defer consideration of a new coverage guidance for this topic until the next two-year review cycle.

Obley reviewed the rescan for Diagnosis of Obstructive Sleep Apnea. Livingston recommended the subcommittee consider updating the current coverage guidance in light of new evidence for home testing devices. The HERC may wish to address clinical pathways to reduce costs for diagnosis for sleep apnea. Livingston said that the recommendation wouldn't be likely to change but there could be recommendations to optimize efficient utilization of these tests. OHP medical directors have requested

review. After brief additional discussion, the subcommittee voted 6-0 (Sorweide absent) to recommend the development of a new coverage guidance on the topic.

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5. SCOPE DEFINITION: Hypofractionated Whole Breast Irradiation for Breast Cancer

Obley reviewed the scope statement, which was created with input from Samuel Wang, a radiation oncologist from OHSU and after public comment. He also reviewed the changes in response to public comments. Based on staff recommendation, the subcommittee members added gender in addition to age to Key Question 2, then approved the revised scope statement by a vote of 6-0.

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6. METABOLIC AND BARIATRIC SURGERY

Coffman introduced Bruce Wolfe, the appointed expert for this topic. He is a retired bariatric surgeon, and also an investigator for research on a nerve stimulation device for treatment of obesity.

Obley reviewed the limitations on the evidence base as reviewed in the previous meeting as well as the newly-added evidence on reoperations. Livingston reviewed the GRADE-informed table and the box recommentations.

Saha noted that in this case values and preferences won't guide whether the procedures are conducted. Instead, society's values and preferences will guide the coverage decision; the varability in patient preferences can be decided by the patient. But society has values around diabetes prevention, the costs and risks of surgery. Ahmann suggested the language on page 30 of the coverage guidance expresses the issues very well. The subcommittee instructed Livingston to edit the values and preferences statements to reflect this before the guidance is posted for comment.

Discussion turned to the coverage recommendations themselves.

Under the first bullet for adult obese patients, the subcommittee removed the words "and <40" to avoid the perception that surgery would not be covered for adults with BMI of 40 or higher."

In addition, the subcommittee discussed the comorbidities other than diabetes which would qualify someone with a BMI of 35-40 for surgery. These are not strictly evidence-based though other payers cover the surgery for patients with varying numbers and types of comorbidities. Those listed in the meeting materials reflected many of the more common ones. Saha noted that we have evidence about hypertension, even though that's not as significant since hypertension has other treatment. Gingerich reviewed some grammatical differences between the last row of the GRADE table and the box and asked permission to align them for clarity. The subcommittee agreed to allow this and also decided to remove dyslipidemia from the list of comorbidities that would allow a person with BMI between 35 and 40 to have surgery, even though some other payers allow surgery for this comorbidity.

Wolfe argued for not specifying specific comorbidities, pointing out that psychosocial reasons have been considered indications. The subcommittee elected to retain its list of comorbidities as edited.

The subcommittee discussed requirements for support groups, surgeon volume and acceptable complication rate. Wolfe recommended that the subcommittee not create requirements based on the limited evidence but instead require the surgery be provided in a facility accredited by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program. It requires outcomes reporting, postoperative support groups and requires adequate surgeon and hospital volume. He said Medicare used to require this but no longer does, and that some private payers are beginning to adopt it. After discussion of the difficulty in evaluating some of the listed criteria, the subcommittee accepted Wolfe's recommendation. Accredited bariatric surgery programs are available in various regions of the state, mitigating the impact of the requirement on patients in many more rural areas, though Labhart expressed concern that Bend is the only program east of the Cascade Mountains. Saha said he doesn't believe anyone is trying to do bariatric surgeries in other parts of Eastern Oregon, but even if there were, the benefit of having surgery available locally would need to be balanced with the risks associated with a lower-volume center. Garside expressed concern that the subcommittee should evaluate the evidence with regard to these factors rather than limiting access based on an external entity, but others doubted that the HERC could monitor these factors as well as a dedicated group. Gingerich asked whether the accredidation includes outpatient surgery centers. Wolfe said there is a separate program for these facilities.

After discussion, the subcommittee removed the requirements that the surgery be performed by an experienced surgeon as well as the requirements for hospital surgical volume and specific postoperative groups and outcomes. These were replaced with a requirement (a weak recommendation) that the surgeries be performed in an accredited facility. Wolfe said that this accreditation would capture the intent of the subcommittee, but without the subcommittee having to stay up-to-date on the intricacies of the evolving evidence base on such requirements.

Livingston reviewed the GRADE table on surgery for children. Saha expressed doubt that waiting until age 18 would create irreversible harm. Wolfe said he didn't object to the summary statement, but referred to a recent study and suggested the subcommittee revisit this topic as well as surgery for BMI under 35 as new evidence becomes available. After discussion the subcommittee agreed not to recommend coverage of this surgery for children.

The subcommittee discussed the recommendation against coverage for complications. Wolfe said this would be problematic for patients with gastric bands which have a high failure rate and risk of severe complications. He noted that other payers separate band removal from other reoperations. Saha questioned whether band removal would be considered bariatric surgery. Wolfe said in some cases it would. Halpin said that other payers do get confused about this. Livingston asked what the indications for removal of a band are. Wolfe said that he will remove them if the patient wants them removed. You don't always know if they plan another surgery at that point. Halpin said there are also complications from bands and associated erosion and scar tissue. There is a risk of irreversible harm from leaving a band in. Wolfe said most payers cover the conversion of a band to a more complicated procedure (e.g. from lap band to sleeve gastrectomy or gastric bypass).

The subcommittee also discussed the issues around patients who convert to another bariatric surgery. Obley said there is low-certainty evidence that patients lose additional weight with these conversion surgeries, and also a higher complication rate. Obley said we don't have direct evidence about whether the benefits of conversion outweigh the harms from the higher complication rate. No data on the numbers of patients with bands are available for Oregon, but Wolfe said the number is much lower than it was a few years ago. Livingston said that access to bariatric surgery is limited as many providers only

take on a limited number of Medicaid patients, and questioned whether patients undergoing an initial surgery should be given priority due to proven benefit. Garside noted we need to take into account the costs of the complications of not having surgery. King suggested allowing accredited centers to make decisions for individual patients about reoperations.

Saha said there are different kinds of conversions—from band to sleeve gastrectomy or from sleeve gastrectomy to bypass or biliopancreatic diversion for example. Obley said there is evidence on these, but there is not much on conversion of gastric bypass to biliopancreatic diversion. He reviewed the weight loss for various conversion surgeries.

Garside asked about recommending against coverage for banding based on the failure rate. The group discussed this but didn't decide to make a change. Wolfe and Halpin said that bands aren't used much anymore because of the complications.

After further discussion, the subcommittee removed the clause recommending against coverage for re-operations based on evidence of additional weight loss, but left the GRADE table row on reoperations and additional evidence as a part of the coverage guidance. The GRADE table will contain a statement that the subcommittee makes no recommendation that coverage criteria for re-operations should be different from primary surgery. The rationale will be based on very low quality evidence that conversion surgeries are associated with increased complications as well as additional weight loss.

The subcommittee addressed recommending coverage for BMI of 30 to 35. There was no discussion and coverage was not recommended for this population.

The subcommittee voted 6-0 (MacKay absent) to post the draft coverage guidance for public comment, with the revisions made during the meeting as well as the additional edits made by staff at the subcommittee's request.

DRAFT HERC Coverage Guidance

Coverage of metabolic and bariatric surgery (including Roux-en-Y gastric bypass, gastric banding, and sleeve gastrectomy) is recommended for:

- Adult obese patients (BMI ≥ 35) with
  - Type 2 diabetes *(strong recommendation)* OR
  - at least two of the following other serious obesity-related comorbidities: hypertension, coronary heart disease, mechanical arthropathy in major weight bearing joint, sleep apnea *(weak recommendation)*
- Adult obese patients (BMI ≥ 40) *(strong recommendation)*

Metabolic and bariatric surgery is recommended for coverage in these populations only when provided in a facility accredited by the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program *(weak recommendation).*

Metabolic and bariatric surgery is not recommended for coverage in:

- Patients with BMI <35, or 35-40 without the defined comorbid conditions above *(weak recommendation)*
- Children and adolescents *(weak recommendation)*

5. ADJOURNMENT

The meeting was adjourned at 3:45 pm. The next meeting is scheduled for February 18, 2016 from 1:00-4:00pm in Room 111-112 of the Wilsonville Training Center of Clackamas Community College.

Section 4.0

VbBS Report

Straightforward Issues—January, 2016

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
50948	Laparoscopy, surgical; ureteroneocystostomy without cystoscopy and ureteral stent placement	184 URETERAL STRICTURE OR OBSTRUCTION; HYDRONEPHROSIS; HYDROURETER	HSD requested that 50948 be paired with N13.5 (Crossing vessel and stricture of ureter without hydronephrosis). 50948 is currently on lines 25, 51, 84, and 91.	Add 50948 to line 184
47535	Conversion of external biliary drainage catheter to internal-external biliary drainage catheter, percutaneous, including diagnostic cholangiography when performed, imaging guidance (eg, fluoroscopy), and all associated radiological supervision and interpretation	320 CANCER OF LIVER	47535 was not added to line 320 during the 2016 CPT code review, although all the other CPT codes in that series (placement/replacement of external biliary drainage catheter) were added to this line.	Add 47535 to line 320
47534-47536	Placement/conversion/ exchange of biliary drainage catheter, percutaneous	84 INJURY TO INTERNAL ORGANS	Only some codes in the 4753x series were added to line 84 during the 2016 CPT code review. The entire series is appropriate for this line	Add 47534-47536 to line 84
27130	Arthroplasty, acetabular and proximal femoral prosthetic replacement (total hip arthroplasty), with or without autograft or allograft	205 CANCER OF BONES	HSD requested that 27130 be added to line 204 to pair with C41.4 (Malignant neoplasm of pelvic bones, sacrum and coccyx). 27130 is currently on lines 85,204,290,360,361,447	Add 27130 to line 205

STRAIGHTFORWARD GUIDELINE CHANGES

January 1, 2016

1) Delete GN16
   a. CF testing is now included in the prenatal and non-prenatal genetic testing guidelines

~~**GUIDELINE NOTE 16, CYSTIC FIBROSIS CARRIER SCREENING**~~

~~*Lines 1,625*~~

~~Cystic fibrosis carrier testing is covered for 1) non-pregnant adults if indicated in the genetic testing algorithm or 2) pregnant women.~~

2) Modify GN65 to include the CPT codes for telephone and email consultations as shown below

GUIDELINE NOTE 65, TELEPHONE AND EMAIL CONSULTATIONS

Included on all lines with evaluation & management (E&M) codes

Telephone and email consultations (CPT 98966-98969) must meet the following criteria:

1) Patient must have a pre-existing relationship with the provider as demonstrated by at least one prior office visit within the past 12 months.
2) E-visits must be provided by a physician or licensed provider within their scope of practice.
3) Documentation should model SOAP charting; must include patient history, provider assessment, and treatment plan; follow up instructions; be adequate so that the information provided supports the assessment and plan; must be retained in the patient's medical record and be retrievable.
4) Telephone and email consultations must involve permanent storage (electronic or hard copy) of the encounter.
5) Telephone and email consultations must meet HIPAA standards for privacy.
6) There needs to be a patient-clinician agreement of informed consent for E-visits by email. This should be discussed with and signed by the patient and documented in the medical record.

Examples of reimbursable telephone and email consultations include but are not limited to:

1) Extended counseling when person-to-person contact would involve an unwise delay.
2) Treatment of relapses that require significant investment of provider time and judgment.
3) Counseling and education for patients with complex chronic conditions.

Examples of non-reimbursable telephone and email consultations include but are not limited to:

1) Prescription renewal.
2) Scheduling a test.
3) Scheduling an appointment.
4) Reporting normal test results.
5) Requesting a referral.
6) Follow up of medical procedure to confirm stable condition, without indication of complication or new condition.
7) Brief discussion to confirm stability of chronic problem and continuity of present management.

Question: Should Barrett's esophagus and esophageal dysplasia be moved to a higher priority line?

Question source: Dr. George Waldmann, CareOregon Medical Director

Issue: In March 2012 the VbBS reviewed the ranking of gastroesophageal reflux disease (GERD). The GERD line was reranked based on the fact that proton pump inhibitor medications (PPIs) are effective in 73% of those empirically treated, but only around 27% in those with endoscopically negative symptoms. The ability of PPIs to prevent dysplasia and esophageal cancer in patients with GERD alone has not been shown in large studies, additionally reducing the effectiveness of treatment ranking for this line. The movement of the GERD line to an unfunded location was effective with the biennial January 1, 2015 Prioritized List.

GERD was further addressed in late 2013, after an HTAS coverage guidance was issued on the use of upper endoscopy. Based on this coverage guidance, HERC adopted a new diagnostic guideline regarding endoscopy for GERD.

> **DIAGNOSTIC GUIDELINE D12, UPPER ENDOSCOPY FOR GERD OR DYSPEPSIA SYMPTOMS**
> Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is covered for:
> 1. Patients less than 50 years of age with persistent symptoms following advice on lifestyle modifications and completion of an appropriate course of twice daily PPI therapy or an H. pylori test and treat protocol.
> 2. Patients 50 years of age and older
> 3. Patients with "alarm symptoms" including, but not limited to, iron deficiency anemia or weight loss
>
> Upper endoscopy is not covered for patients with previous upper endoscopy with non-malignant findings (other than Barrett's esophagus) in the absence of significant new symptoms.
> The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-upper-gerd.aspx

This new guideline required short term PPI therapy prior to EGD; therefore, GERD was re-reviewed in March, 2015 and some GERD diagnoses were moved to a covered line with a note in the treatment description that this line was for short term medical therapy only. A new guideline was adopted to clarify this line distinction.

> Line 385
> Condition: ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS
> Treatment: Short-term medical therapy, Surgical treatment

GUIDELINE NOTE 144, PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Lines 385,516

Short term treatment (up to 8 weeks) of GERD with proton pump inhibitor therapy is included on Line 385. Long term treatment is included on Line 516.

The 2012, 2013 and 2015 discussions did involve discussion of treatment of Barrett's esophagus, which is a advanced form of GERD in which there is pre-cancerous metaplasia of the lower esophagus cells into intestinal epithelial type cells. The Barrett's ICD-9 code was not moved to the upper esophagitis line during the 2015 review. Additionally, there was no discussion about treatment of Barrett's with dysplasia, which is considered a more severe form of Barrett's and has a significantly increased risk of developing into esophageal cancer, particularly for high grade dysphasia. ICD-10 has new diagnosis codes distinguishing these more severe forms of Barrett's, which include low grade or high grade dysplasia. Esophageal dysplasia is normally treated with endoscopic ablation therapy, frequent endoscopies, and long-term PPI therapy. Severe dysplasia may be treated with surgical resection of a portion of the esophagus. These new ICD-10 codes were reviewed during the GI ICD-10 review, but at that time all the codes were on a covered line and no changes were recommended by the GI experts.

During the current review of this topic, HERC staff noted that eosinophilic esophagitis was included on the upper and lower GERD lines. However, review of the treatment of this condition finds that it is treated with allergy medications and dietary changes; it is resistant to PPI therapy in most cases as it is caused by some type of underlying allergic condition. This condition mainly becomes an issue when it causes narrowing of the esophagus; esophageal dilation is the mainstay of treatment for this. The esophageal dilation CPT codes are not included on the upper, covered GERD line.

Current code placement

ICD-10 Code	Code Description	Placement
C15.x	Malignant neoplasm of esophagus	**319** CANCER OF ESOPHAGUS
D00.1	Carcinoma in situ of esophagus	**319**
K20.0	Eosinophilic esophagitis	**385** ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS **516** ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA
K20.8	Other esophagitis	**385, 516**
K20.9	Esophagitis, unspecified	**385, 516**
K21.0	Gastro-esophageal reflux disease with esophagitis	**385, 516**
K21.9	Gastro-esophageal reflux disease without esophagitis	**385, 516**
K22.70	Barrett's esophagus without dysplasia	**516**
K22.710	Barrett's esophagus with low grade dysplasia	**516**
K22.711	Barrett's esophagus with high grade dysplasia	**516**
K22.719	Barrett's esophagus with dysplasia, unspecified	**516**

CPT code	Code description	Line(s)
43216-43217	Esophagoscopy, flexible, transoral; with removal of tumor(s), polyp(s), or other lesion(s) by hot biopsy forceps/snare	**319** CANCER OF ESOPHAGUS **595** SECONDARY AND ILL-DEFINED MALIGNANT NEOPLASMS **642** BENIGN NEOPLASMS OF DIGESTIVE SYSTEM
43229	Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)	**319** **383** ESOPHAGEAL STRICTURE; ACHALASIA **516** ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA **595** **642**
43270	Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s)	**319,595,642**

Note: 43229 and 43270 are used for radiofrequency ablation

Evidence

1) **Rees 2010**, Cochrane review of treatment of Barrett's esophagus PDF not attached due to length. Study found here: http://www.update-software.com/BCP/WileyPDF/EN/CD004060.pdf
    a. N=16 studies (1074 patients)
    b. Medical and surgical interventions to reduce symptoms and sequelae of gastro-oesophageal reflux disease (GORD) did not induce significant eradication of Barrett's oesophagus or dysplasia.
    c. Endoscopic therapies (photodynamic therapy (PDT with aminolevulinic acid or porfimer sodium), argon plasma coagulation (APC) and radiofrequency ablation (RFA)) all induced regression of Barrett's oesophagus and dysplasia.
    d. Radiofrequency ablation resulted in eradication rates of 77% and 86% for Barrett's oesophagus and dysplasia, while those rates were 2%and 21%in the sham treatment group respectively.
    e. Conclusions: Despite their failure to eradicate Barrett's oesophagus, the role of medical and surgical interventions to reduce the troubling symptoms and sequelae of GORD is not questioned. Whether therapies for GORD reduce the cancer risk is not yet known. Ablative therapies have an increasing role in the management of dysplasia within Barrett's and current data would favour the use of radiofrequency ablation compared with photodynamic therapy
2) **Singh 2015**, meta-analysis of treatment of Barrett's - PDF not attached due to length. Study found here: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4199831/
    a. N=7 studies (2813 patients with Barrett's oesophagus (BO), 317 with high grade dysplasia or OAC)
        i. Observational studies. 84.4% of patients were treated with PPIs
    b. On meta-analysis, PPI use was associated with a 71% reduction in risk of OAC and/or BO-HGD in patients with BO (adjusted OR 0.29; 95% CI 0.12 to 0.79).
    c. There was a trend towards a dose–response relationship with PPI use for >2–3 years protective against OAC or BO-HGD (three studies; PPI use >2–3 years vs <2–3 years: OR 0.45 (95% CI 0.19 to 1.06) vs 1.09 (0.47 to 2.56)).
    d. Conclusions Based on meta-analysis of observational studies, the use of PPIs is associated with a decreased risk of OAC and/or BO-HGD in patients with BO. None of the studies showed an increased risk of OAC. PPI use should be considered in BO, and chemopreventive trials of PPIs in patients with BO are warranted

Expert recommendations

1) **NICE, 2010 and 2014** - PDF not attached due to length. Study found here: https://www.nice.org.uk/guidance/ipg496/resources/endoscopic-radiofrequency-

ablation-for-barretts-oesophagus-with-lowgrade-dysplasia-or-no-dysplasia-1899870055700677

a. Barrett's with high grade dysplasia
    i. Endoscopic therapy is recommended for high grade dysplasia
        1. Endoscopic mucosal resection or endoscopic ablation (radiofrequency or photodynamic therapy or argon plasma coagulation)
    ii. Surgical removal of the esophagus can be done for Barrett's with high grade dysplasia
b. Barrett's with low grade dysplasia
    i. Current evidence supports endoscopic radiofrequency ablation, as long as patients have long term follow up
    ii. Based on 2 RCTs (N=336)
        1. 1 trial found reduced rates of progression to adenocarcinoma at 3 year follow up for ablation vs surveillance endoscopy
        2. 1 trial found improved resolution of dysplasia with ablation vs surveillance at 12 months (all pts treated at 12 months, no intent to follow for progression to adenocarcinoma). Less progression seen to high grade dysplasia in the treatment group
c. Barrett's without dysplasia
    i. Evidence does not support radiofrequency ablation
    ii. Case series reviewed
d. Note: medication use (PPI therapy) was not addressed in these guidelines

2) **American College of Gastroenterology 2015** - PDF not attached due to length. Study found here: http://gi.org/wp-content/uploads/2015/11/ACG-2015-Barretts-Esophagus-Guideline.pdf

a. Barrett's esophagus (BE) without dysplasia
    i. Patients with BE should receive once-daily PPI therapy even if no GERD symptoms are present. Routine use of twice-daily dosing is not recommended, unless necessitated because of poor control of reflux symptoms or esophagitis (strong recommendation, moderate level of evidence).
        1. Recommendation based on cohort studies that suggest that subjects with BE maintained on PPI therapy have a decreased risk of progression to neoplastic BE compared with those with either no acid suppressive therapy or those maintained on H 2 RA therapy. Given the low probability of a randomized study of PPI use in BE, decisions regarding this intervention will likely rely on these retrospective data and expert opinion.
        2. A meta-analysis based on 7 studies with 2,813 patients demonstrated a 71% reduced risk of HGD and/or EAC with PPI users (OR 0.3, 95% CI 0.1–0.8).
        3. Risk of progression of BE to dysplasia was found to be 0.33% per year (95% CI 0.28–0.38%), although risk increased with length of

BE segment, age, and other risk factors. Based on a 2012 meta-analysis of 57 studies

ii. Endoscopic surveillance should take place at intervals of 3 to 5 years (strong recommendation, moderate level of evidence)

a. Barrett's with low grade dysplasia without life-limiting comorbidity
    a. endoscopic therapy is considered as the preferred treatment modality, although endoscopic surveillance every 12 months is an acceptable alternative (strong recommendation, moderate level of evidence)
    b. Risk of progression of low grade dysplasia to high grade dysplasia or EAC were 1.7% annually, based on a meta-analysis of 24 studies
b. BE and confirmed high grade dysplasia
    a. endoscopic therapy should be used unless the patient has a life-limiting comorbidity (strong recommendation, high level of evidence)
    b. Risk of progression of high grade dysplasia to EAC was 7-19% annually, depending on the study
c. In patients with dysplastic BE who are to undergo ablative endoscopic therapy for nonnodular disease, radiofrequency ablation is currently the preferred endoscopic ablative therapy (strong recommendation, moderate level of evidence)
d. More frequent endoscopic surveillance is recommended for high grade dysplasia (every 3 months for 1 year, then every 6 months for 1 year, then yearly) and low grade dysplasia (every 6 months for 1 year then yearly) after ablation (conditional recommendation, low level of evidence)

Summary

For Barrett's esophagus without dysplasia, evidence finds that the risk of progression to high grade dysplasia or esophageal cancer is low, although certain risk factors (length of abnormal segment of esophagus, male, age) increase this risk. The use of PPI therapy to prevent the progression of Barrett's to dysplasia or esophageal cancer is debatable based on the current literature; however, observational studies and expert opinion support the use of long term PPI therapy for Barrett's. More frequent endoscopy is also indicated in Barrett's. Endoscopic treatment of Barrett's without dysplasia with radiofrequency ablation or other methods is not supported by the evidence or recommended by expert groups.

For Barrett's with low grade or high grade dysplasia, expert guidelines and moderate quality evidence support treatment with endoscopic radiofrequency ablation and long term PPI therapy. More frequent surveillance endoscopy is also recommended for Barrett's with dysplasia.

Note: K22.71 (Barrett's esophagus with dysplasia) were temporarily added to line 319 CANCER OF ESOPHAGUS and K22.70 (Barrett's esophagus) was temporarily added to line 385 ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS as errata in November, 2015 to allow treatment of this condition prior to the publication of the October 1, 2016 Prioritized List.

HERC staff recommendations:

1) Add K20.0 (Eosinophilic esophagitis) to line 383 ESOPHAGEAL STRICTURE; ACHALASIA and remove from lines 385 ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS and 516 ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA
    a. Main therapy is medical (allergy medications, diet therapy) and esophageal dilation. Dilation CPT codes are available on line 383 but not lines 385 or 516
2) Affirm addition of K22.70 (Barrett's esophagus) to line 385 and remove from line 516
3) Affirm addition of K22.711 (Barrett's esophagus with high grade dysplasia) to line 319 CANCER OF ESOPHAGUS and remove from line 516
    a. Similar to carcinoma in situ (similar prognosis and treatment). All endoscopic and surgical therapies available on line 319

Choose 1 of the 2 options for Barrett's esophagus with low grade or unspecified dysplasia:

Option 1

1) Affirm addition of K22.710 (Barrett's esophagus with low grade dysplasia) and K22.719 (Barrett's esophagus with unspecified dysplasia) to line 319 CANCER OF ESOPHAGUS and remove from line 516 ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA
    a. Has all recommended endoscopic treatments
2) Change the title of line 319 to CANCER OF ESOPHAGUS; BARRETT'S ESOPHAGUS WITH DYSPLASIA
3) Modify GN 144 as shown below

GUIDELINE NOTE 144, PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Lines 385,516

Short term treatment (up to 8 weeks) of GERD without Barrett's (ICD-10 K20.8, K20.9, K21.0, K21.9) with proton pump inhibitor therapy is included on Line 385. Long term treatment is included on Line 516.

Long term proton pump inhibitor therapy is included on line 385 for Barrett's esophagus (ICD-10 K22.70).

Option 2

1) Add K22.710 (Barrett's esophagus with low grade dysplasia) and K22.719 (Barrett's esophagus with unspecified dysplasia) to line 385 ESOPHAGITIS; ESOPHAGEAL AND INTRAESOPHAGEAL HERNIAS and reverse the errata addition of these codes to line 319

CANCER OF ESOPHAGUS. Remove K22.710 and K22.719 from line 516 ESOPHAGITIS AND GERD; ESOPHAGEAL SPASM; ASYMPTOMATIC DIAPHRAGMATIC HERNIA

2) Add CPT 43229 and 43270 (Esophagoscopy/ Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s)) to line 385
3) Modify GN 144 as shown below

GUIDELINE NOTE 144, PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Lines 385,516

Short term treatment (up to 8 weeks) of GERD without Barrett's (ICD-10 K20.8, K20.9, K21.0, K21.9) with proton pump inhibitor therapy is included on Line 385. Long term treatment is included on Line 516.

Long term proton pump inhibitor therapy is included online 385 for Barrett's esophagus with or without dysplasia (ICD-10 K22.70, K22.71).

CPT 43229 and 43270 are included on line 385 only for pairing with Barrett's esophagus with dysplasia (ICD-10 K22.71) and only when used for endoscopic radiofrequency ablation.

Other Diseases of the Lips and Oral Mucosa

Question:

1) How should the ICD-10 diagnosis codes for various lip and oral mucosa conditions be prioritized?
2) How should GN113 be modified to clarify the coverage intent?

Question source: HERC staff

Issues: The ICD-10 ENT group reviewed the current lines for oral leukoplakia (OL) and carcinoma in situ (line 168) of the mouth, as well as various other lines. The review group made various recommendations for code movement and line title changes, but not all the changes for line 168 were carried out. The major change for this line was to remove the oral leukoplakia ICD-10 code (K13.21 Leukoplakia of oral mucosa, including tongue) and place on an uncovered line. The experts felt that there was currently no evidence of effective treatments of this condition to prevent the development of oral cancer. The line title was supposed to be changed to reflect this removal; however, in error, this change was not made and has been changed as an errata: **168** ~~LEUKOPLAKIA AND~~ CARCINOMA IN SITU OF UPPER AIRWAY, INCLUDING ORAL CAVITY.

HERC staff confirmed the movement of leukoplakia to an uncovered line. A 2006 Cochrane review (Lodi et al 2006) found no effective non-surgical treatments for this condition. A 2014 review of surgical interventions (Balasundarum et al 2014) found no RCTs which addressed whether surgery reduces the rate of malignant transformation of leukoplakia, and reported "growing evidence that surgical removal, in some cases, may be associated with future recurrence and malignant development." Arduino et al (2013) found that "the vast majority of OLs follow a benign course and do not progress into a cancer, and no widely accepted and/or validated clinical and/or biological factors can predict malignant transformation." Based on this evidence, HERC staff is comfortable with the movement of leukoplakia to an uncovered line. Biopsy of the lesions to rule out malignancy or carcinoma in situ would still be covered as diagnostic.

Several additional issues were found during this review.

1) The wording of GN113 needs to be clarified. The current wording refers to "subdiagnoses" of K13.0 when what is intended is diagnoses that use that code. A whole range of diagnoses use K13.0, including abscess, cheilitis, hypertrophy, cellulitis and mucocele of the lip. The current guideline wording is unclear.
2) Several codes in the K13 series were found to be on incorrect lines on staff review. These codes were all reviewed during the ICD-10 ENT review, and the current placements were specifically done by that review group. However, HERC staff review respectfully disagrees with several of the recommended placements of that review group. Two of the codes are dental and deal with denture issues; these codes were suggested for movement to uncovered lines after consultation with Dr. Bruce Austin, the OHA dental director.

ICD-10 code	Code description	Current line(s)	Comments	HERC staff recommended placement
K13.0	Diseases of lips	**210** SUPERFICIAL ABSCESSES AND CELLULITIS **585** CANDIDIASIS OF MOUTH, SKIN AND NAILS		**210, 585**
K13.1	Cheek and lip biting	**579** STOMATITIS AND OTHER DISEASES OF ORAL SOFT TISSUES		**579**
K13.21	Leukoplakia of oral mucosa, including tongue	**623** BENIGN LESIONS OF TONGUE	Moved by ICD-10 ENT review. See discussion above	**623**
K13.22	Minimal keratinized residual ridge mucosa	**623**	Moved by ICD-10 ENT review. Not a tongue condition. Dental ridge condition	**579** STOMATITIS AND OTHER DISEASES OF ORAL SOFT TISSUES
K13.23	Excessive keratinized residual ridge mucosa	**168** ~~LEUKOPLAKIA AND~~ CARCINOMA IN SITU OF UPPER AIRWAY, INCLUDING ORAL CAVITY	Left by ICD-10 ENT review. This is also a dental ridge condition, caused by dentures	**579** STOMATITIS AND OTHER DISEASES OF ORAL SOFT TISSUES
K13.24	Leukokeratosis nicotina palati	**168**	Left by ICD-10 ENT review. Condition caused by heat from smoking, reversible with smoking cessation.	**579** STOMATITIS AND OTHER DISEASES OF ORAL SOFT TISSUES
K13.29	Other disturbances of oral epithelium, including tongue	**168**	Left by ICD-10 ENT review. Diagnoses using this code include erythroplakia (premalignant), focal epithelial hyperplasia, and leukoedema.	**168**
K13.3	Hairy leukoplakia	**623**	Moved by ICD-10 ENT review. Epstein-Barr infection, not a cancer precursor	**623**

HERC staff recommendations:

1) Affirm the change in line title for line 168 ~~LEUKOPLAKIA AND~~ CARCINOMA IN SITU OF UPPER AIRWAY, INCLUDING ORAL CAVITY as recommended by the ICH-10 ENT reviewers but never implemented
2) Add K13.2 (Minimal keratinized residual ridge mucosa) to line 579 STOMATITIS AND OTHER DISEASES OF ORAL SOFT and remove from line 623 BENIGN LESIONS OF TONGUE
3) Add K13.23 (Excessive keratinized residual ridge mucosa) to line 579 and remove from line 168
4) Add K13.24 (Leukokeratosis nicotina palati) to line 579 STOMATITIS AND OTHER DISEASES OF ORAL SOFT and remove from line 168
5) Modify GN113 as shown below

GUIDELINE NOTE 113, DISEASES OF LIPS

Lines 210,585

ICD-10-CM code K13.0 (Diseases of lips) is included on Line 210 only for treatment of abscess or cellulitis of the lips. All other ~~subdiagnoses~~ diagnoses coded using K13.0 ~~under this code~~ are included on Line 585.

Issue: the scoliosis line has only PT and surgery codes. The intent of the Low Back Conditions Taskforce was to have the pain resulting from scoliosis treated just like any other back pain, and the line was added to the medical low back pain guideline at the November, 2015 VBBS meeting. The medical back guideline contains coverage for acupuncture and chiropractic care; the CPT codes for these treatments are not included on the scoliosis line, however. Scoliosis diagnosis codes are not included on the general medical back conditions line.

Recommendation:

1) Add acupuncture and chiropractic CPT codes to line 366 SCOLIOSIS
    a. Acupuncture: 97810-97814
    b. Osteopathic manipulation: 98925- 98929
    c. Chiropractic: 98940-98942

Back Line Straightforward Changes

1) Add M96.5 (Postradiation scoliosis) to line 366 SCOLIOSIS and remove from lines 407 CONDITIONS OF THE BACK AND SPINE and 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS.
2) Add Q06.0 (Amyelia), Q06.1 (Hypoplasia and dysplasia of spinal cord), Q06.3 (Other congenital cauda equina malformations) and Q06.8 (Other specified congenital malformations of spinal cord) to line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
    a. Not currently on any surgical lines
    b. All are currently on the medical back line and the dysfunction lines
3) Add Q67.5 (Congenital deformity of spine) and Q76.3 (Congenital scoliosis due to congenital bony malformation) to line 366 SCOLIOSIS and delete from the applicable lines in the set of lines including 407 CONDITIONS OF THE BACK AND SPINE and 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS and 665 MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
    a. Codes for congenital scoliosis
4) Add S23.101, S23.111, S23.121, S23.123, S23.131, S23.133, S23.141, S23.143, S23.151, S23.153, S23.161, S23.163, S23.171 (Dislocation of thoracic vertebra), and S33.101, S33.111, S33.121, S33.131, S33.141 (Dislocation of lumbar vertebra) to line 482 CLOSED DISLOCATIONS/FRACTURES OF NON-CERVICAL VERTEBRAL COLUMN WITHOUT NEUROLOGIC INJURY OR STRUCTURAL INSTABILITY and remove from any of the following lines on which they appear: 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS and/or 665 MISCELLANEOUS CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
    a. Leave on line 407 CONDITIONS OF THE BACK AND SPINE
5) Remove M46.1 (Sacroiliitis, not elsewhere classified) from line 532.
    a. Will remain on line 407 only. No surgical treatments for this condition
6) Add S33.8XXA (Sprain of other parts of lumbar spine and pelvis, initial encounter) to line 407 CONDITIONS OF THE BACK AND SPINE and remove from line 611 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR
7) Remove M42.1 (Adult osteochondrosis of spine) and M42.9 (Spinal osteochondrosis, unspecified) from line 530 DEFORMITIES OF UPPER BODY AND ALL LIMBS and add to line 407
    a. On line 532 as well
8) Remove M43.3 (Recurrent atlantoaxial dislocation with myelopathy), M43.4 (Other recurrent atlantoaxial dislocation), M43.5x2 (Other recurrent vertebral dislocation, cervical region) and M43.5x3 (Other recurrent vertebral dislocation, cervicothoracic region) from any of the following lines on which they currently appear: line 364 DEFORMITY/CLOSED DISLOCATION OF MAJOR JOINT AND RECURRENT JOINT DISLOCATIONS, and/or line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS. Add these codes to line 154 CERVICAL VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR CLOSED; OTHER VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR UNSTABLE; SPINAL CORD INJURIES WITH OR WITHOUT EVIDENCE OF VERTEBRAL INJURY
    a. Leave on line 407 CONDITIONS OF THE BACK AND SPINE
9) Remove M43.5X3, M43.5x4, M43.5X5, M43.5X6, M43.5X7, M43.5X8, M43.5X9, (Other recurrent vertebral dislocation, non cervical) from lines 364 DEFORMITY/CLOSED DISLOCATION OF MAJOR JOINT AND RECURRENT JOINT DISLOCATIONS, and line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS. Add these codes to line 482 CLOSED

DISLOCATIONS/FRACTURES OF NON-CERVICAL VERTEBRAL COLUMN WITHOUT NEUROLOGIC INJURY OR STRUCTURAL INSTABILITY

   a. Leave on line 407 CONDITIONS OF THE BACK AND SPINE

10) Remove M45 (Ankylosing spondylitis) from line 50 RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHROPATHIES
   a. Keep on lines 407 and 532
   b. Add M45.9 (Ankylosing spondylitis of unspecified sites in spine) to line 407 CONDITIONS OF THE BACK AND SPINE
11) Remove M46.0 (Spinal enthesopathy) form line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
   a. Remains on lines 490 PERIPHERAL ENTHESOPATHIES and 508 PERIPHERAL ENTHESOPATHIES
12) Remove M46.2x (Osteomyelitis of vertebra) from line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS. This condition is on the osteomyelitis line with appropriate surgeries.
13) Remove M46.3 (Infection of intervertebral disc (pyogenic)) from line 259 CHRONIC OSTEOMYELITIS and line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS and add to line 51 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS
14) Remove M46.5 (Other infective spondylopathies) from line 50 RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHROPATHIES and add to line 407 CONDITIONS OF THE BACK AND SPINE
15) Remove M46.80 (Other specified inflammatory spondylopathies, site unspecified) and M46.90 (Unspecified inflammatory spondylopathy, site unspecified) from line 50 RHEUMATOID ARTHRITIS AND OTHER INFLAMMATORY POLYARTHROPATHIES and add to line 407 CONDITIONS OF THE BACK AND SPINE
   a. Also on line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
16) Remove M46.81-M46.89 (Other specified inflammatory spondylopathies) and M46.91-M46.99 (Unspecified inflammatory spondylopathy) from line 50
   a. Already on line 407 and 532
17) Remove M48.8X (Other specified spondylopathies) from line 467 OSTEOARTHRITIS AND ALLIED DISORDERS and add to line 407 CONDITIONS OF THE BACK AND SPINE
18) Remove M53.2X9 (Spinal instabilities, site unspecified) from line 663 MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY and add to line 407 CONDITIONS OF THE BACK AND SPINE
   a. Already on line 351
19) Remove M99.80 (Other biomechanical lesions of head region) from line 261 DEFORMITIES OF HEAD and line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS and add to line 543 TENSION HEADACHES
20) Remove M99.81-M99.85 (Other biomechanical lesions of spine) from line 663 MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY and add to line 407 CONDITIONS OF THE BACK AND SPINE
21) Remove M99.86-M99-.89 (Other biomechanical lesions of extremity or trunk) from line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
22) Add Q06.2 (Diastematomyelia) and Q06.9 (Congenital malformation of spinal cord, unspecified) to line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
   a. Also on dysfunction lines and line 407

Back Line Straightforward Changes

23) Remove S13.0XXA (Traumatic rupture of cervical intervertebral disc, initial encounter) from line 520 and add to line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS. This diagnosis is also on line 407
24) Add S34.3XXA (Injury of cauda equina, initial encounter) to line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
25) Add Z47.82 (Encounter for orthopedic aftercare following scoliosis surgery) to line 366 SCOLIOSIS and remove from lines 351 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS and 407 CONDITIONS OF THE BACK AND SPINE

Question: should artificial disc CPT codes be added to the covered surgical back line?

Question source: HERC staff

Issue: during the back line taskforce meetings and subsequent VBBS and HERC discussions of back condition treatments, artificial discs were not discussed. GN101 regarding artificial discs was also not reviewed. This guideline is based on a coverage guidance review. The CPT codes for placement, revision and removal of artificial discs were placed on the scoliosis line and the uncovered surgical back line at the March, 2015 VBBS/HERC meeting as part of the back line revision process. These artificial discs are not used for scoliosis surgery.

HERC staff recommendations:

1) Add CPT 22586-22865 (placement, revision and removal of total disc arthroplasty (artificial disc), anterior approach, cervical and lumbar) to line 351 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS
2) Remove CPT 22586-22865 from line 366 SCOLIOSIS
3) Leave CPT 22586-22865 on line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
4) Affirm GN101 as shown below

GUIDELINE NOTE 101, ARTIFICIAL DISC REPLACEMENT

Lines 351 and 532

Artificial disc replacement (CPT 22856-22865) is included on these lines as an alternative to fusion only when all of the following criteria are met:

Lumbar artificial disc replacement

1) Patients must first complete a structured, intensive, multi-disciplinary program for management of pain, if covered by the agency;
2) Patients must be 60 years or under;
3) Patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes:
    - Failure of at least six months of conservative treatment
    - Skeletally mature patient
    - Replacement of a single disc for degenerative disc disease at one level confirmed by patient history and imaging

Cervical artificial disc replacement

1) Patients must meet FDA approved indications for use and not have any contraindications. FDA approval is device specific but includes:
    - Skeletally mature patient
    - Reconstruction of a single disc following single level discectomy for intractable symptomatic cervical disc disease (radiculopathy or myelopathy) confirmed by patient findings and imaging.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-artificial-disc-replace.aspx

Question: how should the new surgical back conditions guideline be modified to indicate that surgeries on the lower (uncovered) line are included on that low line only after 6 months of conservative therapy?

Question source: HERC staff

Issue: The surgical back guideline has a clause which requires that all surgeries included on the lower, uncovered back surgery line need to have 6 months of conservative therapy prior to being eligible for surgery. Some CCOs and others have interpreted this clause to mean that after 6 months of conservative therapy, these conditions have COVERED surgeries. The intent of the back lines taskforce was to have these surgeries on the uncovered line and require 6 months of conservative care before they could be eligible for surgery through the co-morbidity rule. These conditions are not meant to pair with surgeries other than through the co-morbidity rule, or if the Legislature funds lines down to 532.

On review, HERC staff feel that all elective surgical back procedures should have 6 months of conservative therapy prior to their coverage. Two options for revising this guideline are possible: 1) requiring all elective procedures to have 6 months of conservative care. This change would theoretically not apply to the upper surgical line, as these surgeries are urgent by definition. However, this change could be interpreted by some CCOs as applying to some of the surgeries on the upper surgical line. The other possibility is 2) delete the clause and add no other change. This would remove the confusing language and clarify that the surgeries on the lower line are not covered except in exceptional circumstances.

HERC staff recommendations:

1) Correct the confusing clause regarding the lower surgical line
    a. Option 1: Delete the clause in red below and make no other changes
    b. Option 2: delete the clause in red below and add the clause in blue
2) Adopt the deletions of incorrect codes in red below
    a. ICD-9 721.1 does not code for spinal stenosis
    b. Remove final x's from ICD-10 codes, as this is not standard

GUIDELINE NOTE 37, SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS

Lines 351, 532

Surgical consultation/consideration for surgical intervention are included on these lines only for patients with neurological complications, defined as showing objective evidence of one or more of the following:

A) Markedly abnormal reflexes
B) Segmental muscle weakness
C) Segmental sensory loss
D) EMG or NCV evidence of nerve root impingement
E) Cauda equina syndrome
F) Neurogenic bowel or bladder
G) Long tract abnormalities

Elective surgical procedures are only included on these lines after the patient has completed at least 6 months of conservative treatment, provided according to Guideline Note 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE.

Spondylolithesis (ICD-9 738.4, 756.11-756.12 / ICD-10 M43.1~~x~~, Q76.2) is included on line 351 only when it results in spinal stenosis with signs and symptoms of neurogenic claudication. Otherwise, these diagnoses are included on line 532.

Surgical correction of spinal stenosis (ICD-9 ~~721.1,~~ 723.0, 724.0x / ICD-10 M48.0~~x~~) is only included on line 351 for patients with:

1) MRI evidence of moderate to severe central or foraminal spinal stenosis AND
2) A history of neurogenic claudication, or objective evidence of neurologic impairment consistent with MRI findings.

Only decompression surgery is covered for spinal stenosis; spinal fusion procedures are not covered for this diagnosis. Otherwise, these diagnoses are included on line 532.

~~For conditions on line 532, surgical interventions may only be considered after the patient has completed at least 6 months of conservative treatment, provided according to Guideline Note 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE~~.

The following interventions are not covered due to lack of evidence of effectiveness for back pain, with or without radiculopathy:

- facet joint corticosteroid injection
- prolotherapy
- intradiscal corticosteroid injection
- local injections
- botulinum toxin injection
- intradiscal electrothermal therapy
- therapeutic medial branch block
- radiofrequency denervation
- radiofrequency denervation
- sacroiliac joint steroid injection
- coblation nucleoplasty
- percutaneous intradiscal radiofrequency thermocoagulation

Diagnostic Imaging for Back Pain Issue Summary

Question: Should Diagnostic Guideline D4 Advanced Imaging for Low Back Pain be modified to 1) restore the requirement for neurologic changes to be present for lumbar MRI and 2) specify when repeat MRIs are appropriate?

Question source: QHOC Medical Directors

Issue: There are concerns raised by CCO Medical Directors regarding the newly revised diagnostic guideline for advanced imaging for low back pain. The revised guideline no longer requires objective evidence of neurologic compromise for coverage of a back MRI. This change was made to bring the MRI guideline into agreement with the definition of neuropathy as including radiating pain which was adopted for the epidural steroid injection (ESI) guideline. The epidural steroid injection guideline was changed to agree with the AHRQ definition of radiculopathy that was used to generathe evidence that these injections are effective. ESI is mainly used for treatment of radiating pain, and significant neurologic compromise is a contraindication. MRI is required by most interventionalists prior to ESI. Therefore, the MRI guideline needed to be broadened to allow imaging for radiating pain alone. Of note, the surgical back guideline maintains the older definition of requiring neurologic compromise prior to allowing surgery.

There was extensive discussion in the back pain taskforce, VBBS and HERC about including coverage for epidural steroid injections for lumbar back pain. The back pain taskforce did not strongly feel that these injections should be covered, and wanted to allow one injection only if it allowed a patient to more fully participate in active types of therapy such as PT. At the March and May, 2015 meetings, VBBS considered the task force recommendation, as well as the previously adopted HERC coverage guidance recommendation. The coverage guidance recommendation on lumbar epidural injections was "For radicular low back pain, epidural steroid injections are recommended for coverage for patients with persistent radiculopathy due to herniated lumbar disc; it is recommended that shared decision-making regarding epidural steroid injection include a specific discussion about inconsistent evidence showing moderate short-term benefits, and lack of long-term benefits. If an epidural steroid injection does not offer benefit, repeated injections are not recommended for coverage." The underlying evidence regarding ESI was not fully discussed or presented during the VBBS or HERC 2015 meetings. VBBS was given several options for ESI, including non-coverage, limiting coverage to the lower surgical back line, and covering on the upper medical back line with a guideline. The final decision from VBBS/HERC was to include epidural steroid injections on the medical back line. A guideline was adopted, which included coverage for radicular pain as defined by the AHRQ evidence review.

Further input on the need for MRI prior to ESI was obtained from Dr. Tim Keenan, the neurosurgical member of the Back Conditions Taskforce. Dr. Keenan feels that MRI needs to be done prior to ESI to locate the anatomic area that needs injection and to rule out contraindications such as tumors. This is standard of care. ESI is most effective

for isolated pain, but can be used for pain with minor muscle weakness. Major muscle weakness or bowel/bladder dysfunction are contraindications to ESI. Dr. Keenan indicated that most private insurers will not cover MRI until 6 weeks of PT has been completed.

The Medical Directors would like to have clarity about the necessity of a neurologic exam to determine imaging appropriateness, as well as language on the appropriateness of repeat MRIs. Additionally, the changes to the MRI guideline will result in many more MRIs being allowed and result in a substantial increase in costs and HERC staff feels that allowing additional MRIs was not the actual intent of the Commission in make the guideline note change.

Currently, with the new guideline MRI is covered for

- Radiculopathic signs present >1 month
    - Radiculopathic signs are defined for the purposes of this guideline as pain, weakness, or sensory deficits, in a nerve root distribution
        - BUT Only if patient is a potential candidate for surgery or, if indicated, lumbar epidural steroid injection (see guideline note 105)
    - Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness
        - BUT Only if patient is a potential candidate for surgery or, if indicated, lumbar epidural steroid injection (see guideline note 105)
    - Spinal stenosis > 1 month
        - BUT Only if patient is a potential candidate for surgery

Current Prioritized List guideline:
DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no "red flag" conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table. Electromyelography (CPT 96002-4) is not covered for non-specific low back pain.

Table D4
Low Back Pain - Potentially Serious Conditions ("Red Flags") and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Cancer	• History of cancer with new onset of LBP	MRI	ESR
	• Unexplained weight loss • Failure to improve after 1 month • Age >50 years • Symptoms such as painless neurologic deficit, night pain or pain increased in supine position	Lumbosacral plain radiography	
	• Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	• Fever • Intravenous drug use • Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	• Urinary retention • Motor deficits at multiple levels • Fecal incontinence • Saddle anesthesia	MRI	None
Vertebral compression fracture	• History of osteoporosis • Use of corticosteroids • Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	• Morning stiffness • Improvement with exercise • Alternating buttock pain • Awakening due to back pain during the second part of the night • Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	• Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month • Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	• Radiculopathic signs[2] present >1 month • Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI[3]	Consider EMG/NCV
Spinal stenosis	• Radiating leg pain • Older age • Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None
	• Spinal stenosis symptoms present >1 month	MRI[4]	Consider EMG/NCV

[1] Level of evidence for diagnostic evaluation is variable

[2] Radiculopathic signs are defined for the purposes of this guideline ~~is defined~~ as ~~the presence of~~ ~~as in Guideline Note 37 with~~ ~~any of the following:~~ pain, weakness, or sensory deficits, in a nerve root distribution

~~A. Markedly abnormal reflexes~~
~~B. Segmental muscle weakness~~
~~C. Segmental sensory loss~~
~~D. EMG or NCV evidence of nerve root impingement~~
~~E. Cauda equina syndrome,~~
~~F. Neurogenic bowel or bladder~~
~~G. Long tract abnormalities~~

[3] Only if patient is a potential candidate for surgery or, if indicated, lumbar epidural steroid injection (see guideline note 105)

[4] Only if patient is a potential candidate for surgery

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders. CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-adv-imaging-low-back.aspx

GUIDELINE NOTE 37, SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS

Lines 351, 532

Surgical consultation/consideration for surgical intervention are included on these lines only for patients with neurological complications, defined as showing objective evidence of one or more of the following:

A) Markedly abnormal reflexes
B) Segmental muscle weakness
C) Segmental sensory loss
D) EMG or NCV evidence of nerve root impingement
E) Cauda equina syndrome
F) Neurogenic bowel or bladder
G) Long tract abnormalities

Spondylolithesis (ICD-9 738.4, 756.11-756.12 / ICD-10 M43.1x, Q76.2) is included on line 351 only when it results in spinal stenosis with signs and symptoms of neurogenic claudication. Otherwise, these diagnoses are included on line 532.

Surgical correction of spinal stenosis (ICD-9 721.1, 723.0, 724.0x / ICD-10 M48.0x) is only included on line 351 for patients with:

1) MRI evidence of moderate to severe central or foraminal spinal stenosis AND
2) A history of neurogenic claudication, or objective evidence of neurologic impairment consistent with MRI findings.

Only decompression surgery is covered for spinal stenosis; spinal fusion procedures are not covered for this diagnosis. Otherwise, these diagnoses are included on line 532.

For conditions on line 532, surgical interventions may only be considered after the patient has completed at least 6 months of conservative treatment, provided according to Guideline Note 56, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE.

The following interventions are not covered due to lack of evidence of effectiveness for back pain, with or without radiculopathy:

- facet joint corticosteroid injection
- prolotherapy
- intradiscal corticosteroid injection
- local injections
- botulinum toxin injection
- intradiscal electrothermal therapy
- therapeutic medial branch block
- radiofrequency denervation
- sacroiliac joint steroid injection
- coblation nucleoplasty
- percutaneous intradiscal radiofrequency thermocoagulation
- radiofrequency denervation

GUIDELINE NOTE 105, EPIDURAL STEROID INJECTIONS FOR LOW BACK PAIN

Line 407

Epidural lumbar steroid injections (CPT 62311, 64483, 64484) are included on this line for patients with persistent radiculopathy due to herniated lumbar disc, where radiculopathy is defined as lower extremity pain in a nerve root distribution, with or without weakness or sensory deficits. ~~showing objective evidence of one or more of the following:~~

~~A) Markedly abnormal reflexes~~
~~B) Segmental muscle weakness~~
~~C) Segmental sensory loss~~
~~D) EMG or NCV evidence of nerve root impingement~~

One epidural steroid injection is included on ~~these lines~~ this line; a second epidural steroid injection may be provided after 3-6 months only if objective evidence of 3 months of sustained pain relief was provided by the first injection. It is recommended that shared decision-making regarding epidural steroid injection include a specific discussion about inconsistent evidence showing moderate short-term benefits, and lack of long-term benefits. Epidural lumbar steroid injections are not included on ~~these lines~~ this line for spinal stenosis or for patients with low back pain without radiculopathy. Epidural steroid injections are only included on this line when the patient is also participating in an active therapy such as physical therapy or home exercise therapy.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-percutaneous-low-back.aspx

Evidence for epidural steroid injections

1) **AHRQ 2015**, technology assessment for injections for low back pain (PDF not attached due to length. Study found here: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0073206/pdf/PubMedHealth_PMH0073206.pdf)
    a. N=78 RCTs for epidural injections
    b. For epidural corticosteroid injections versus placebo interventions for radiculopathy, the only statistically significant effects were on mean improvement in pain at immediate-term followup (weighted mean difference [WMD] –7.55 on a 0 to 100 scale, 95% CI –11.4 to –3.74) (strength of evidence [SOE]: moderate), mean improvement in function at immediate-term followup when an outlier trial was excluded (standardized mean difference [SMD] –0.33, 95% CI –0.56 to –0.09) (SOE: low), and risk of surgery at short-term followup (relative risk [RR] 0.62, 95% CI 0.41 to 0.92) (SOE: low). The magnitude of effects on pain and function was small, did not meet predefined thresholds for minimum clinically important differences, and there were no differences on outcomes at longer-term followup. Evidence on effects of different injection techniques, patient characteristics, or comparator interventions estimates was limited and did not show clear effects. Trials of epidural corticosteroid injections for radiculopathy versus nonplacebo interventions did not clearly demonstrate effectiveness (SOE: insufficient to low).
    c. Evidence was limited for epidural corticosteroid injections versus placebo interventions for spinal stenosis (SOE: low to moderate) or nonradicular back pain (SOE: low), but showed no differences in pain, function, or likelihood of surgery.
    d. Serious harms from injections were rare in randomized trials and observational studies, but harms reporting was suboptimal (SOE: low).
    e. **Conclusions:** Epidural corticosteroid injections for radiculopathy were associated with immediate improvements in pain and might be associated with immediate improvements in function, but benefits were small and not sustained, and there was no effect on long-term risk of surgery. Evidence did not suggest that effectiveness varies based on injection technique, corticosteroid, dose, or comparator. Limited evidence suggested that epidural corticosteroid injections are not effective for spinal stenosis or nonradicular back pain.
2) **Staal 2011,** Cochrane review on injections for subacute and chronic low back pain
    a. N=18 trials (1179 participants) involving epidural steroid injections or facet joint injections
    b. Overall, the results indicated that there is no strong evidence for or against the use of any type of injection therapy.

c. **Authors' conclusions:** There is insufficient evidence to support the use of injection therapy in subacute and chronic low-back pain. However, it cannot be ruled out that specific subgroups of patients may respond to a specific type of injection therapy.

3) **Bickett 2015,** systematic review of effect of ESI on surgery rates
   a. N=26 studies
   b. For studies examining ESI effect on surgery as the primary outcome, moderate evidence that patients who received ESI were less likely to undergo surgery than those who received control treatment.
   c. For studies examining surgery as a secondary outcome, ESI demonstrated a trend to reduce the need for surgery for short-term (<l1 year) outcomes (risk ratio, 0.68; 95% confidence interval, 0.41–1.13; p5.14) but not long-term outcomes (0.95, 0.77–1.19, p5.68).
   d. Secondary analyses provided low-level evidence suggesting that between one-third and half of patients considering surgery who undergo ESI can avoid surgery.
   e. CONCLUSIONS: Epidural steroid injections may provide a small surgery-sparing effect in the short term compared with control injections and reduce the need for surgery in some patients who would otherwise proceed to surgery.

Other policies

1) NICE 2009
   a. Recommends against use of epidural steroid injections for initial treatment of low back pain

Staff summary:
Epidural steroid injections do not appear to provide clinically significant pain relief or functional improvement in the short or long term, and are unlikely to reduce rates of surgery. From AHRQ: "The magnitude of effects on pain and function was small, did not meet predefined thresholds for minimum clinically important differences, and there were no differences on outcomes at longer-term followup."

Current coverage of ESI requires that MRIs be available for the evaluation of any type of low back pain with radiating pain. It is standard of care to obtain an MRI prior to ESI, and ESI is most commonly used for radiating pain without neurologic change. The liberalization of MRI criteria for low back pain will result in a vast increase in coverage and will have substantial cost impact.

Overall, when the additional cost of MRIs are factored in, ESI does not appear to be a cost-effective therapy. Removal of coverage for ESI would allow restoration of the previous guideline definition of radiculopathy.

HERC Staff Recommendations:

1) Remove coverage for epidural steroid injections
    a. Remove CPT 64483 (Injection(s), anesthetic agent and/or steroid, transforaminal epidural, with imaging guidance (fluoroscopy or CT); lumbar or sacral, single level) and 64484 (each additional level) from line 407 CONDITIONS OF THE BACK AND SPINE
    b. Add epidural steroid injections to the list of non-covered procedures in GUIDELINE NOTE 37, SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS
    c. Remove 64484 from line 159 HERPES ZOSTER; HERPES SIMPLEX AND WITH NEUROLOGICAL AND OPHTHALMOLOGICAL COMPLICATIONS
        i. 64483 is not on that line and therefore additional levels cannot be injected
    d. Place 64483 and 64484 on the Services Recommended for Non-Coverage table
    e. Delete guideline note 105 EPIDURAL STEROID INJECTIONS FOR LOW BACK PAIN
2) Modify DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN as shown below
    a. Adds wording regarding when repeat MRI imaging is appropriate
    b. Restores previous requirements for imaging for low back pain to patients with neurologic changes

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no "red flag" conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table. Repeat imaging is only covered when there is a substantial clinical change (e.g. progressive neurological deficit) or new clinical indication for imaging (i.e. development of a new red flag condition). Repeat imaging for acute exacerbations of chronic radiculopathic pain is not covered.

Electromyelography (CPT 96002-4) is not covered for non-specific low back pain.

Table D4
Low Back Pain - Potentially Serious Conditions ("Red Flags") and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
Cancer	• History of cancer with new onset of LBP	MRI	ESR
	• Unexplained weight loss • Failure to improve after 1 month	Lumbosacral plain radiography	

Possible cause	Key features on history or physical examination	Imaging[1]	Additional studies[1]
	• Age >50 years • Symptoms such as painless neurologic deficit, night pain or pain increased in supine position		
	• Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	• Fever • Intravenous drug use • Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	• Urinary retention • Motor deficits at multiple levels • Fecal incontinence • Saddle anesthesia	MRI	None
Vertebral compression fracture	• History of osteoporosis • Use of corticosteroids • Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	• Morning stiffness • Improvement with exercise • Alternating buttock pain • Awakening due to back pain during the second part of the night • Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	• Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month • Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	• Radiculopathic signs[2] present >1 month • Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI[3]	Consider EMG/NCV
Spinal stenosis	• Radiating leg pain • Older age • Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None
	• Spinal stenosis symptoms present >1 month	MRI[3]	Consider EMG/NCV

[1] Level of evidence for diagnostic evaluation is variable

[2] Radiculopathic signs are defined for the purposes of this guideline as ~~pain, weakness, or sensory deficits, in a nerve root distribution~~ the presence of any of the following:

A. Markedly abnormal reflexes
B. Segmental muscle weakness
C. Segmental sensory loss
D. EMG or NCV evidence of nerve root impingement
E. Cauda equina syndrome,
F. Neurogenic bowel or bladder
G. Long tract abnormalities

[3] Only if patient is a potential candidate for surgery ~~or, if indicated, lumbar epidural steroid injection (see guideline note 105)~~

~~[4] Only if patient is a potential candidate for surgery~~

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders. CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-adv-imaging-low-back.aspx

Intrathecal Pump Guideline

Question: Should we delete the intrathecal pump guideline (GN72)?

Question source: HERC staff

Issue: Coverage for placement of intrathecal pumps was removed for back pain and soft tissue pain indications in January, 2009. At that meeting, the HOSC/HSC determined that coverage of maintenance and removal of previously implanted pumps was to be continued. GN72 was adopted to clarify that pump maintenance was only covered for pumps placed before the insertion coverage change. The GN states that only pumps placed before 2009 will have maintenance covered; however, OHP patients have come onto OHP coverage with a pump already placed during previous insurance coverage that will need maintenance.

The CPT codes for the insertion, removal and maintenance of intrathecal pumps appear on a number of lines, including cancer lines and dysfunction lines. GN72 has never applied to these lines. Intrathecal pumps are used for chemotherapy or for antispasmotic medication therapy on these lines, and this has been determined to be an appropriate use of these pumps.

The CPT codes in question (62367-62370) can be paired with ICD-10 code Z45.49 (Encounter for adjustment and management of other implanted nervous system device) which is found on 3 lines on the Prioritized List. These CPT codes can also pair with diagnosis codes, such as cerebral palsy.

Current guideline note
GUIDELINE NOTE 72, ELECTRONIC ANALYSIS OF INTRATHECAL PUMPS

Lines ~~374,545,~~ 351, 366, 532, 612

Electronic analysis of intrathecal pumps, with or without programming (CPT codes 62367-~~62368~~62370), is included on these lines only for pumps implanted prior to April 1, 2009

(changes noted above are from the back lines review)

Intrathecal Pump Guideline

HERC staff recommendations:

1) Delete GN72
    a. Is interfering with maintenance of current patient pumps for patients obtaining pumps outside of OHP after 2009
2) Remove 62367 (Electronic analysis of programmable, implanted pump for intrathecal or epidural drug infusion (includes evaluation of reservoir status, alarm status, drug prescription status); without reprogramming or refill), 62368 (with reprogramming), 62369 (with reprogramming and refill), and 62370 (with reprogramming and refill (requiring skill of a physician or other qualified health care professional)) from lines 351* CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS, 366* SCOLIOSIS, and 532* CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS, and 607 DISORDERS OF SOFT TISSUE
    a. *implementation of these lines is delayed
    b. No longer on the "stand in" back lines
3) Add ICD-10-CM Z45.49 (Encounter for adjustment and management of other implanted nervous system device) to line 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
4) Add 62367-62370 (Electronic analysis of programmable, implanted pump for intrathecal or epidural drug infusion) to line 290 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
    a. #3 and #4 allow maintenance of pumps inserted for diagnoses not covered for this type of pump on the Prioritized List for patients with pumps inserted prior to being OHP patients

Tobacco use disorder and elective surgery

Question: Should a guideline be adopted about tobacco cessation and elective surgery?

Question source: QHOC Medical Directors

Issue: There are poorer healing outcomes associated with patients who actively use tobacco products who are undergoing surgery. The QHOC Medical Directors are interested in whether the evidence suggests specific criteria for poorer outcomes which may lead to coverage decisions about elective surgeries.

At the November 12, 2015 VbBS meeting there was a review of the background, evidence and proposed guidelines. There was a proposal to add a smoking cessation requirement for the surgical treatment of erectile dysfunction. Members requested staff to review the proposed guideline note on elective surgeries with QHOC medical directors and bring the topic back for discussion.

Current Prioritized List Status

GUIDELINE NOTE 100, SMOKING AND SPINAL FUSION
Lines 51,154,204,258,374,412,484,533,588
Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking for 6 months prior to the planned procedure. Patients should be given access to appropriate smoking cessation therapy.

GUIDELINE NOTE 112, LUNG VOLUME REDUCTION SURGERY
Line 288
Lung volume reduction surgery (LVRS, CPT 32491, 32672) is included on Line 288 only for treatment of patients with radiological evidence of severe bilateral upper lobe predominant emphysema (diagnosis code ICD-10-CM J43.9/ICD-9-CM 492.0, 492.8) and all of the following:

1. BMI ≤31.1 kg/m2 (men) or ≤32.3 kg/m 2 (women)
2. Stable with ≤20 mg prednisone (or equivalent) dose a day
3. Pulmonary function testing showing
   a. Forced expiratory volume in one second (FEV 1) ≤ 45% predicted and, if age 70 or older, FEV 1≥ 15% predicted value
   b. Total lung capacity (TLC) ≥ 100% predicted post-bronchodilator
   c. Residual volume (RV) ≥ 150% predicted post-bronchodilator
4. PCO 2, ≤ 60 mm Hg (PCO 2, ≤ 55 mm Hg if 1-mile above sea level)
5. PO 2, ≥ 45 mm Hg on room air (PO 2, ≥ 30 mm Hg if 1-mile above sea level)
6. Post-rehabilitation 6-min walk of ≥ 140 m
7. Non-smoking for 6 months prior to surgery, as shown by cotinine level

The procedure must be performed at an approved facility (1) certified by the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) under the

LVRS Disease Specific Care Certification Program or (2) approved as Medicare lung or heart-lung transplantation hospitals. The patient must have approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation. The patient must have approval for surgery by cardiologist if any of the following are present: unstable angina; left-ventricular ejection fraction (LVEF) cannot be estimated from the echocardiogram; LVEF <45%; dobutamineradionuclide cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia (>5 premature ventricular contractions per minute; cardiac rhythm other than sinus; premature ventricular contractions on EKG at rest).

GUIDELINE NOTE 8, BARIATRIC SURGERY

Lines 30,594

…Excerpt

> Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from nicotine and illicit drugs.

Line: 5

Condition: TOBACCO DEPENDENCE (See Guideline Notes 4,64,65)
Treatment: MEDICAL THERAPY/BRIEF COUNSELING NOT TO EXCEED 10 FOLLOW-UP VISITS OVER 3 MONTHS
ICD-9: 305.1,649.00-649.04
CPT: 96127-96154,97810-97814,98966-98969,99078,99201-99215,99224,99324-99350,99366,99406,99407,99441-99449,99487-99498,99605-99607
HCPCS: D1320,G0425-G0427,G0436,G0437,G0459,G0463,G0466,G0467,G0469, G0470,G9016,H0038,S9453

Line: 529

Condition: SEXUAL DYSFUNCTION (See Guideline Notes 64,65)
Treatment: PSYCHOTHERAPY, MEDICAL AND SURGICAL TREATMENT
ICD-10: F52.0-F52.1,F52.21-F52.4,F52.6-F52.9,N52.01-N52.9,N53.11-N53.19,R37
CPT: 54400-54417,90785,90832-90840,90846-90853,90882,90887,93980,93981,98966-98969,99051,99060,99070,
99078,99201-99239,99281-99285,99291-99360,99366,99374,99375,99379-99404,99408-99412,99429-99449,
99471-99476,99487-99498,99605-99607
HCPCS: G0176,G0177,G0396,G0397,G0406-G0408,G0425-G0427,G0459,G0463,G0466,G0467,G0469,G0470,H0004,
H0023,H0032-H0035,H0038,H2011,H2014,H2027,H2032,S9484,T1016

GUIDELINE NOTE 4, TOBACCO DEPENDENCE

Line 5

Pharmacotherapy and behavioral counseling are included on this line, alone or in combination, for at least 2 quit attempts per year. A minimum of four counseling sessions of at least 10 minutes each (group or individual, telephonic or in person) are included for each quit attempt. More intensive interventions and group therapy are likely to be the most effective behavioral interventions.

Inclusion on this line follows the minimum standard criteria as defined in the Oregon Public Health Division "Standard Tobacco Cessation Coverage" (based on the Patient Protection and Affordable Care Act), available here:
https://public.health.oregon.gov/PreventionWellness/TobaccoPrevention/Pages/pubs.aspx

Evidence Summary

MED, 2013 Report

Clinical review:
There are many studies linking perioperative smoking with surgical complications and poor post-operative outcomes (such as wound healing, cardiac and pulmonary complications, and death). There is also associated longer hospital stays, need for revision, and increased health care costs.

Current medical literature is abundant with studies that demonstrate perioperative smoking is strongly linked to surgical complications and poor post-operative outcomes. Adverse post-operative outcomes include impaired wound and tissue healing, and cardiopulmonary complications such as respiratory failure, cardiac arrest, and myocardial infarction (Balaji 2008; Centers for Medicare and Medicaid Services [CMS] 2013; Finks 2011; Katznelson 2011; Khullar 2013; Rinker 2013; Safadi 2009; Turan 2011). Additionally, smokers may be up to twice as likely to experience pneumonia, unplanned intubation, mechanical ventilation, and death after surgery due to preoperative smoking (Khullar 2013). These outcomes can often result in the need for prolonged hospital stays, and the potential for surgical revision (Katznelson 2011; Turan 2011). They may put active smokers at higher risk for surgical complications, and elevate healthcare costs over time (CMS 2013; Khullar 2013; Turan 2011).

Perioperative smoking has been shown to adversely affect outcomes associated with a wide range of surgeries including cardiac, vascular, thoracic, general, urologic, and plastic reconstructive procedures (Katznelson 2011; Turan 2011).

Thomsen, 2014 (not included in packet due to study's length)

1. Cochrane systematic review of preoperative smoking cessation interventions

2. 13 trials involving 2010 participants
3. Overall quality of evidence moderate due to small sample size
4. Intensive interventions appeared to reduce any complications (RR 0.42; 95% CI 0.27 to 0.65, 2 trials, 210 participants) and on wound complications (RR 0.31; 95% CI 0.16 to 0.62, 2 trials, 210 participants). For brief interventions, where the impact on smoking had been smaller, there was no evidence of a reduction in complications (RR 0.92; 95% CI 0.72 to 1.19, 4 trials, 493 participants) for any complication (RR 0.99; 95% CI 0.70 to 1.40, 3 trials, 325 participants) for wound complications. The trial of varenicline did not detect an effect on postoperative complications (RR 0.94; 95% CI 0.52 to 1.72, 1 trial, 286 participants).
    a. Intensive interventions were defined as multisession face to face counseling
    b. Intensive interventions were effective at cessation at the time of surgery (pooled risk ratio (RR) 10.76; 95% confidence interval (CI) 4.55 to 25.46, two trials, 210 participants) whereas brief interventions were not shown to be (RR 1.30; 95% CI 1.16 to 1.46, 7 trials, 1141 participants).
    a. A single trial did not show evidence of benefit of a scheduled reduced smoking intervention.
5. Conclusions: preoperative smoking interventions providing behavioural support and offering NRT increase short-term smoking cessation and may reduce postoperative morbidity. One trial of varenicline begun shortly before surgery has shown a benefit on long-term cessation but did not detect an effect on early abstinence or on postoperative complications. The optimal preoperative intervention intensity remains unknown. Based on indirect comparisons and evidence from two small trials, interventions that begin four to eight weeks before surgery, include weekly counselling and use of NRT, are more likely to have an impact on complications and on long-term smoking cessation.

Khullar, 2012.

1. Clinical review on impact of smoking on surgical procedures
2. Most trials have found that 4 to 8 weeks of smoking abstinence substantially reduces perioperative complications and the need for repeat surgery

Sorenson, 2012

1. Systematic review and metanalysis
2. 140 cohort studies including 479,150 patients
3. Results: The pooled adjusted odds ratios (95% CI) were 3.60 (2.62-4.93) for necrosis, 2.07 (1.53-2.81) for healing delay and dehiscence, 1.79 (1.57-2.04) for surgical site infection, 2.27 (1.82-2.84) for wound complications, 2.07 (1.23-3.47) for hernia, and 2.44 (1.66-3.58) for lack of fistula or bone healing. Former smokers and patients who never smoked were compared in 24 studies including 47,764 patients, and former smokers and current smokers were compared in 20 studies including 40,629 patients. The pooled unadjusted odds ratios were 1.30 (1.07-1.59) and 0.69 (0.56-0.85), respectively, for healing complications

combined. In 4 randomized controlled trials, smoking cessation intervention reduced surgical site infections (odds ratio, 0.43 [95% CI, 0.21-0.85]), but not other healing complications (0.51 [0.22-1.19]).

Corbett, 2012

1. Clinical review of tobacco cessation and solid organ transplantation
2. 1996 Consensus guidelines from US and Europe state that candidates for lung transplantation must have been free of substance addiction (including alcohol, tobacco, and narcotics) for at least 6 months. More recently, they have changed to make smoking a relative contraindication
3. In heart transplantation, smokers have:
    a. Reduced life expectance, increased rates of coronary artery disease, increased malignancy, increased all cause and cardiac death, postoperative renal dysfunction, longer hospital stays, skin cancer. And other solid organ cancers. Limits life expectance.
4. In kidney transplantation smokers have:
    a. Increased rates of allograft loss, death, transplant failure, diabetes, cardiovascular events, and cancer
5. In liver transplantation smokers have:
    a. increased overall mortality, cardiovascular-related mortality, and sepsis-related mortality, and biliary complication rates
    b. one conflicting single center study exists

NICE Guideline - Osteoarthritis: Care and Management in Adults. Patient-specific factors (including age, sex, smoking, obesity and comorbidities) should not be barriers to referral for joint surgery. **[2008, amended 2014]**

Other state policies:

- Alabama requires patients to be tobacco free for 8 weeks prior to gastric bypass surgery
- West Virginia requires patients to be tobacco free for 6 months prior to gastric bypass surgery
- Other states (Washington, California, and Louisiana) have more vague language about being substance free, which may or may not include tobacco

Other Payers

Aetna

(2012) – Heart-Lung Transplantation – smokers must be abstinent for three months before consideration for candidacy;

(2013a) – Lung Transplantation – smokers must be abstinent for six months before consideration for candidacy;

(2013b) – Obesity Surgery – patients suggested to stop smoking six to eight weeks before surgery;

(2013c) – Pulmonary Rehabilitation – candidate must not have a recent history of smoking and/or has quit for at least three months;

(2013d) – Spinal Surgery: Laminectomy and Fusion – no specified discontinuation time, but cites smoking as an absolute contraindication that would preclude a patient from eligibility; and

(2013e) – Surgical/Penile Revascularization for Erectile Dysfunction – patient must not be actively smoking (no time limits specified).

BlueCross BlueShield (Anthem; Alabama) o Anthem BCBS (2012) – identifies smoking as a major contraindication/risk factor for electrical bone growth stimulation.

Alabama BCBS (2012) – requires patients to be tobacco-free for a minimum of eight weeks prior to surgery for bariatric procedures.

Cigna lists tobacco-free policies on two procedures:

(2007) – Lumbar Fusion for Spinal Instability and Degenerative Disc Conditions – smoking identified as a major contraindication and associated with risk of pseudoarthritis; and

(2009) – Lung Volume Reduction Surgery – smoking cessation required for at least six months.

UniCare (2012) – has tobacco-free policies for lung volume reduction surgery requiring candidates to be abstinent from smoking for at least four months.

HERC Staff Assessment

There is a strong association with smoking and increased morbidity with surgical procedures. The Prioritized List currently has restrictions on surgery requiring smoking cessation for at least 6 months for lung volume reduction surgery, bariatric surgery, and for spinal fusion. Other elective surgeries may result in improved post-surgical outcomes with similar smoking cessation requirements based on limited evidence. NICE specifically recommends not having smoking status being a barrier to joint replacement

referral. There are effective interventions to improve cessation rates that are covered for OHP.

A number of QHOC medical directors were asked their opinion and there were mixed views. Some arguing for cessation prior to elective surgery, others arguing for requiring intervention but had concerns about implementation. No arguments for no guideline note were made.

QHOC medical directors have requested greater clarity about defining the frequency of cotinine testing.

Tobacco use disorder and elective surgery

HERC Staff Recommendations:

1) Continue requiring smoking cessation 6 months prior to lung volume reduction surgery, bariatric surgery, and spinal fusion.

2) Discuss adding a Guideline Note:

CHOICE 1

ANCILLARY GUIDELINE NOTE XXX, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES

Participation in intensive smoking cessation interventions (multiple sessions of behavioral counseling +/- nicotine replacement) in active tobacco users are required after the referral for surgery and at least 4 weeks prior to elective surgical procedures.

Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month tobacco abstinence requirements.

CHOICE 2

ANCILLARY GUIDELINE NOTE XXX, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES

Smoking cessation is required prior to elective surgical procedures for active tobacco users. Cessation is required at least 4 weeks prior to the procedure, as shown by a cotinine level.

Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month tobacco abstinence requirements.

CHOICE 3 – Do not add a guideline on smoking cessation and elective surgical procedures

3) Modify guideline notes 8, 100, and 112

A) to be consistent in requiring cotinine level testing, and
B) consider adding language about the frequency of testing.

GUIDELINE NOTE 100, SMOKING AND SPINAL FUSION

Lines 51,154,204,258,374,412,484,533,588

Non-emergent spinal arthrodesis (CPT 22532-22634) is limited to patients who are non-smoking for 6 months prior to the planned procedure, as shown by negative cotinine levels (at least one level within one month of the quit date and one level within one month of surgery). Patients should be given access to appropriate smoking cessation therapy.

GUIDELINE NOTE 8, BARIATRIC SURGERY

Lines 30,594

…Excerpt

Must remain free of abuse of or dependence on alcohol during the six-month period immediately preceding surgery. No current use of nicotine or illicit drugs and must remain abstinent from their use during the six-month observation period. Testing will, at a minimum, be conducted within one month of the surgery to confirm abstinence from ~~nicotine and~~ illicit drugs. Tobacco abstinence to be confirmed in active smokers by negative cotinine levels (at least one level within one month of the quit date and one level within one month of surgery).

GUIDELINE NOTE 112, LUNG VOLUME REDUCTION SURGERY

Line 288

Lung volume reduction surgery (LVRS, CPT 32491, 32672) is included on Line 288 only for treatment of patients with radiological evidence of severe bilateral upper lobe predominant emphysema (diagnosis code ICD-10-CM J43.9/ICD-9-CM 492.0, 492.8) and all of the following:

1. BMI ≤31.1 kg/m2 (men) or ≤32.3 kg/m 2 (women)
2. Stable with ≤20 mg prednisone (or equivalent) dose a day
3. Pulmonary function testing showing
   a. Forced expiratory volume in one second (FEV 1) ≤ 45% predicted and, if age 70 or older, FEV 1≥ 15% predicted value
   b. Total lung capacity (TLC) ≥ 100% predicted post-bronchodilator
   c. Residual volume (RV) ≥ 150% predicted post-bronchodilator
4. PCO 2, ≤ 60 mm Hg (PCO 2, ≤ 55 mm Hg if 1-mile above sea level)
5. PO 2, ≥ 45 mm Hg on room air (PO 2, ≥ 30 mm Hg if 1-mile above sea level)
6. Post-rehabilitation 6-min walk of ≥ 140 m
7. Non-smoking for 6 months prior to surgery, as shown by negative cotinine levels (at least one level within one month of the quit date and one level within one month of surgery).

The procedure must be performed at an approved facility (1) certified by the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) under the LVRS Disease Specific Care Certification Program or (2) approved as Medicare lung or heart-lung transplantation hospitals. The patient must have approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist post-rehabilitation. The patient must have approval for surgery by cardiologist if any of the following are present: unstable angina; left-ventricular ejection fraction (LVEF) cannot be estimated from the echocardiogram; LVEF <45%; dobutamine radionuclide cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia (>5 premature ventricular contractions per minute; cardiac rhythm other than sinus; premature ventricular contractions on EKG at rest).

4) Add a new guideline about surgical treatment of erectile dysfunction based on the November VbBS discussion.

   GUIDELINE NOTE XXX SMOKING AND SURGICAL TREATMENT OF ERECTILE DYSFUNCTION

   Line 526

   Surgical treatment of erectile dysfunction is only included on this line when patients are non-smoking for 6 months prior to surgery, as shown by negative cotinine levels (at least one level within one month of the quit date and one level within one month of surgery).

5) Do not add a requirement for transplantation. While there is certainly evidence of poorer outcomes associated with smoking and transplant, these criteria are managed by the transplant centers and through OARs; a guideline note may be redundant and/or unnecessary.

Section 5.0

Coverage Guidance Rescan

2015

Carotid Endarterectomy for Carotid Artery Stenosis – 2015 Rescanning Summary

Subcommittee: Health Technology Assessment Subcommittee (HERC approved December 2013)

HTAS Recommendation: Reaffirm the existing coverage guidance and reconsider the need to update it during the regular two-year review cycle.

Bottom Line: There is new (but limited and contradictory) summary evidence and guidelines about the comparative effectiveness of CEA vs carotid stenting or optimal medical treatment.

Coverage Recommendation (Box Language)

Carotid endarterectomy is recommended for coverage for patients who are symptomatic (recent transient ischemic attack or ischemic stroke) and who have 70-99% carotid stenosis without near-occlusion (*strong recommendation*).

For patients with 50 – 69% carotid stenosis who are symptomatic despite optimal medical management, carotid endarterectomy is recommended for coverage (*weak recommendation*).

Carotid endarterectomy is not recommended for coverage for symptomatic patients with less than 50% carotid stenosis (*strong recommendation*).

Carotid endarterectomy is recommended for coverage for patients with asymptomatic carotid stenosis of at least 60% only for those who do not tolerate (or have contraindications to) best current medical therapy (*weak recommendation*).

Screening for asymptomatic carotid artery stenosis in the general primary care population is not recommended (*strong recommendation*).

Scope Statement

Population description	Adults with carotid stenosis with or without recent symptoms of cerebral ischemia *Population scoping notes: None*
Intervention(s)	Carotid endarterectomy *Intervention exclusions: None*
Comparator(s)	Optimal medical therapy, carotid stenting

Outcome(s) (up to five)	**Critical:** All-cause mortality, cerebrovascular accidents **Important:** Transient ischemic attacks, development/progression of vascular dementia, quality of life *Considered but not selected for GRADE table: Need for reintervention*
Key questions	1. What is the comparative effectiveness of carotid endarterectomy for treatment of symptomatic or asymptomatic carotid stenosis? 2. What degree of carotid stenosis predicts clinical utility of carotid endarterectomy? 3. What are the harms of carotid endarterectomy? 4. Under what circumstances should carotid endarterectomy be covered for asymptomatic patients (i.e., when stenosis is found as an incidental finding)?

Original Evidence Sources

Chambers B. R., & Donnan, G. (2005). Carotid endarterectomy for asymptomatic carotid stenosis. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD001923. DOI: 10.1002/14651858.CD001923.pub2. Retrieved from http://summaries.cochrane.org/CD001923/carotid-endarterectomy-for-asymptomaticcarotid-stenosis

Publication status and date: Edited (no change to conclusions), published in Issue 4, 2008.

Grant, E. G., Benson, C. B., Moneta, G. L., Alexandrov, A. V., Baker, J. D., Bluth, E. I., … Zierler, E. (2003). Carotid artery stenosis: Gray-scale and Doppler US diagnosis – Society of Radiologists in Ultrasound Consensus Conference. *Radiology, 229*(2), 340-346. Retrieved from http://pubs.rsna.org/doi/pdf/10.1148/radiol.2292030516

Raman, G., Moorthy, D., Nadar, N, Dahabreh, I., O'Donnell, T., Thaler, D., … Kitsios, J. D. (2013). Management strategies for asymptomatic carotid stenosis. *Annals of Internal Medicine, 158*(9), 676-685. DOI: 10.7326/0003-4819-158-9-201305070-00007.

Rerkasem, K., & Rothwell, P. M. (2011). Carotid endarterectomy for symptomatic carotid stenosis. *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD001081. DOI: 10.1002/14651858.CD001081.pub2.

U.S. Preventive Services Task Force. (2007). Screening for carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*, *147*(12), 854-859. DOI: 10.7326/0003-4819-147-12-200712180-00005.

Scanning Results

1. Antoniou, G. A., Georgiadis, G. S., Georgakarakos, E. I., Antoniou, S. A., Bessias, N., Smyth, J. V., … Lazarides. M. K. (2013). Meta-analysis and meta-regression analysis of outcomes of carotid endarterectomy and stenting in the elderly. *Journal of the American Medical Association Surgery, 148*(12), 1140-1152. DOI: 10.1001/jamasurg.2013.4135.

Citation 1 is a large meta-analysis of 44 studies (comprising nearly 600,000 patients) of CEA or carotid stenting. It provides new information on the comparative effectiveness of CEA vs carotid stenting and suggests that the best intervention may vary depending on the age of the patient.

2. Bekelis, K., Moses, Z., Missios, S., Desai, A., & Labropoulos, N. (2013). Indications for treatment of recurrent carotid stenosis. *British Journal of Surgery, 100*(4), 440-7. DOI: 10.1002/bjs.9027.

Citation 2 is a systematic review of 50 studies reporting on indications for CEA or carotid stenting in patients with recurrent carotid stenosis after an initial CEA. It does not provide information that would change the coverage guidance.

3. Eckstein, H. H., Kühnl, A., Dörfler, A., Kopp, I.B., Lawall, H., & Ringleb, P. A. (2013). The diagnosis, treatment and follow-up of extracranial carotid stenosis: A multidisciplinary German-Austrian guideline based on evidence and consensus. *Deutsches Ärzteblatt International, 110*(26-27), 468-76. DOI: 10.3238/arztebl.2013.0468.

Citation 3 is a systematic review and multidisciplinary evidence-based guideline from Germany and Austria. The recommendations generally comport with the existing HERC coverage guidance, although they do not require a trial of optimal medical therapy before considering CEA in asymptomatic individuals with >60% stenosis (while also acknowledging that controlled trials of various treatment options for asymptomatic patients are needed). It also offers guidance on situations in which carotid stenting may be preferable to CEA.

4. Fink, H. A., Hemmy, L. A., MacDonald, R., Carlyle, M. H., Olson, C. M., Dysken, M. W., … Wilt, T. J. (2014). Cognitive outcomes after cardiovascular procedures in older adults: A systematic review. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id97ta.pdf

Citation 4 is an AHRQ review of literature on cognitive outcomes after cardiovascular procedures in older adults. It concludes that CEA and endovascular interventions for carotid revascularization result in similar intermediate-term cognitive outcomes.

5. Fokkema, M., Vrijenhoek, J. E., Den Ruijter, H. M., Groenwold, R. H., Schermerhorn, M. L., Bots, M. L., … De Borst, G. J., TREAT CARE Study Group. (2015). Stenting versus endarterectomy for restenosis following prior ipsilateral carotid endarterectomy: An individual patient data meta-analysis. *Annals of Surgery*, *261*(3), 598-604). DOI: 10.1097/SLA.0000000000000799.

Citation 5 is a meta-analysis of individual-level patient data on CEA vs carotid stenting for treatment of ipsilateral restenosis after prior CEA. The short-term outcomes of stroke, death, and restenosis were similar between the two interventions.

6. Guay, J., & Ochroch, E. A. (2012). Carotid endarterectomy plus medical therapy or medical therapy alone for carotid artery stenosis in symptomatic or asymptomatic patients: a meta-analysis. *Journal of Cardiothoracic and Vascular Anesthesia, 26*(5), 835-844. DOI: 10.1053/j.jvca.2012.01.044.

Citation 6 is a systematic review and meta-analysis of RCTs comparing CEA and medical therapy in patients with symptomatic or asymptomatic carotid stenosis. It concludes that CEA is beneficial for symptomatic patients with >50% stenosis, but offers no benefit in asymptomatic patients. The latter conclusion is potentially at odds with the current HERC coverage guidance.

7. Haedersdal, C., Sondergaard, M. P., & Olsen, T. S. (2012). Costs of secondary prevention of stroke by carotid endarterectomy. *European Neurology, 68*(1), 42-46. DOI: 10.1159/000337864.

Citation 7 is a cost-effectiveness study of CEA in the Danish National Health Service. Any conclusions are probably too indirect to influence the HERC coverage guidance.

8. Jonas, D. E., Feltner, C., Amick, H. R., Sheridan, S., Zheng, Z. J., Watford, D. J., … Harris, R. (2014). Screening for Asymptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis for the U.S. Preventive Services Task Force. Evidence Synthesis No. 111. AHRQ Publication No. 13-05178-EF-1. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://www.uspreventiveservicestaskforce.org/Home/GetFile/1/1534/cases111/pdf

9. Jonas, D. E., Feltner, C., Amick, H. R., Sheridan, S., Zheng, Z. J., Watford, D. J., … Harris, R. (2014). Screening for asymptomatic carotid artery stenosis: a systematic review and meta-analysis for the US Preventive Services Task Force. *Annals of Internal Medicine, 161*(5), 336-346. DOI: 10.7326/M14-0530.

Citations 8 and 9 comprise updated evidence and USPSTF guidelines regarding screening for carotid stenosis in asymptomatic individuals. They support the current HERC coverage guidance that does not recommend screening in asymptomatic individuals.

10. Khan, A. A., Chaudhry, S. A., Sivagnanam, K., Hassan, A. E., Suri, M. F., & Qureshi, A. I. (2012). Cost-effectiveness of carotid artery stent placement versus endarterectomy in patients with carotid artery stenosis. *Journal of Neurosurgery, 117*(1), 89-93. DOI: 10.3171/2012.3.JNS111266.

Citation 10 is an economic evaluation of carotid stenting with an embolic-prevention device vs CEA for patients at average surgical risk. Because stenting produces only marginally greater QALYs compared with CEA at greater cost, the ICER for stenting is >$200,000. It would provide new contextual information on resource use if the coverage guidance is updated.

11. LeFevre, M. L., on behalf of the U.S. Preventive Services Task Force. (2014). Screening for asymptomatic carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine, 161*(5), 356-362. DOI: 10.7326/M14-1333

Citations is updated evidence and USPSTF guidelines regarding screening for carotid stenosis in asymptomatic individuals, which supports the current HERC coverage guidance that does not recommend screening in asymptomatic individuals.

12. Liu, Z. J., Fu, W. G., Guo, Z. Y., Shen, L. G., Shi, Z. Y., & Li, J. H. (2012). Updated systematic review and meta-analysis of randomized clinical trials comparing carotid artery stenting and carotid endarterectomy in the treatment of carotid stenosis. *Annals of Vascular Surgery, 26*(4), 576-590. DOI: 10.1016/j.avsg.2011.09.009.

Citation 12 is an updated systematic review and meta-analysis of RCTs comparing CEA and carotid stenting. Its overall conclusion is that stenting is inferior to CEA with respect to stroke or death, but because of a lower incidence of myocardial infarction, stenting may be preferable in selected patients.

13. Mandavia, R., Qureshi, M. I., Dharmarajah, B., Head, K., & Davies, A. H. (2014). Safety of carotid intervention following thrombolysis in acute ischaemic stroke. *European Journal of Vascular and Endovascular Surgery, 48*(5), 505-512. DOI: 10.1016/j.ejvs.2014.08.012.

Citation 13 summarizes evidence on the appropriate use and timing of CEA after thrombolysis for acute ischemic stroke. Generally, the study supports the safety of CEA within 14 days of an acute ischemic stroke treated with thrombolysis, though the quality of evidence is low.

14. Paraskevas, K. I., Lazaridis, C., Andrews, C. M., Veith, F. J., & Giannoukas, A. D. (2014). Comparison of cognitive function after carotid artery stenting versus carotid endarterectomy. *European Journal of Vascular and Endovascular Surgery, 47*(3), 221-231. DOI: 10.1016/j.ejvs.2013.11.006.

Citation 14 is a systematic review of studies comparing cognitive function after CEA vs carotid stenting. Due to a high degree of heterogeneity among the included studies, meta-analysis was not performed and definite conclusions could not be drawn.

15. Skelly, A. C., Brodt, E. D., Hashimoto, R. E., Schenk-Kisser, J. M., Junge, M., & Holmer, H. (2013). Stenting for treatment of atherosclerotic stenosis of the extracranial carotid arteries or intracranial arteries. Olympia, WA: Washington Health Technology Assessment Program. Retrieved from http://www.hca.wa.gov/hta/documents/cas_final_report_081513.pdf

Citation 15 is a health technology assessment of carotid stenting performed for the Washington HTA. On the basis of these results, the Washington HTA has opted to cover carotid stenting for symptomatic patients with >50% stenosis or asymptomatic patients with >80% stenosis AND who are deemed to be at high operative risk for CEA. This information would potentially change HERC coverage guidance.

16. Sternbergh, W. C., Crenshaw, G. D., Bazan, H. A., & Smith, T. A. (2012). Carotid endarterectomy is more cost-effective than carotid artery stenting. *Journal of Vascular Surgery, 55*(6), 1623-1628. DOI: 10.1016/j.jvs.2011.12.045.

Citation 16 is a cost-effectiveness analysis of CEA vs carotid stenting based on a retrospective case series at a single institution. This study design is inadequate to inform HERC coverage guidance.

17. Thapar, A., Garcia Mochon, L., Epstein, D., Shalhoub, J., & Davies, A. H. (2013). Modelling the cost-effectiveness of carotid endarterectomy for asymptomatic stenosis. *British Journal of Surgery, 100*(2), 231-239. DOI: 10.1002/bjs.8960.

Citation 17 is a cost-effectiveness study of CEA for asymptomatic individuals in the British National Health Service. Any conclusions are probably too indirect to influence the HERC coverage guidance.

18. Vilain, K. R., Magnuson, E. A., Li, H., Clark, W. M., Begg, R. J., Sam, A. D., … Cohen, D. J. (2012). Costs and cost-effectiveness of carotid stenting versus endarterectomy for patients at standard surgical risk: results from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke, 43*(9), 2408-2416. DOI: 10.1161/STROKEAHA.112.661355.

Citation 18 is an economic evaluation of carotid stenting vs CEA for patients at average surgical risk. It concludes that there are trivial differences in the long-term costs between the two interventions. It would provide new contextual information on resource use if the coverage guidance is updated.

19. Wang, L., Liu, X. Z., Liu, Z. L., Lan, F. M., Shi, W. C., Liu, J., & Zhang, J. N. (2013). A meta-analysis of carotid endarterectomy versus stenting in the treatment of symptomatic carotid stenosis. *Chinese Medical Journal, 126*(3), 532-535. PMID: 23422120

Citation 19 is a meta-analysis of 8 trials comparing CEA vs carotid stenting in symptomatic patients. This appears to be a low-quality systematic review and would probably not be included for review in an update of the HERC coverage guidance.

20. Yong, Y. P., Saunders, J., Abisi, S., Sprigg, N., Varadhan, K., MacSweeney, S., & Altaf, N. (2013). Safety of carotid endarterectomy following thrombolysis for acute ischemic stroke. *Journal of Vascular Surgery, 58*(6), 1671-1677. DOI: 10.1016/j.jvs.2013.05.093

Citation 20 summarizes evidence on the appropriate use and timing of CEA after thrombolysis for acute ischemic stroke. Generally, the study supports the safety of CEA within 14 days of an acute ischemic stroke treated with thrombolysis, though the quality of evidence is low.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "carotid endarterectomy" and "carotid stenosis." Searches of core sources were limited to citations published after 2011 (the last search date of original evidence sources).

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2012 (last search dates of original evidence sources).

Searches for clinical practice guidelines were limited to those published since 2012 (last search date of coverage guidance). A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Cervical Cancer Screening

EbGS rescan recommendation

EbGS recommends retiring this coverage guidance and deferring to the United States Preventive Services Task Force (USPSTF).

The HERC Coverage Guidance, Routine Cervical Cancer Screening, approved in 2013, aligned with the USPSTF recommendations. EbGS recommends retiring the coverage guidance because the USPSTF now defines use of preventive services for the Essential Health Benefits. The Essential Health Benefits provide minimum coverage standards on preventive services for most health plans in the United States.

Continuous Glucose Monitoring in Diabetes Mellitus – 2015 Rescanning Summary

Subcommittee: Health Technology Assessment Subcommittee (HERC approved May 2013)

HTAS Recommendation: Develop a new coverage guidance to update this topic.

Bottom Line: Despite publication of several RCTs since the 2013 coverage guidance, the body of evidence on continuous glucose monitoring (CGM) remains mixed. The use of real-time continuous glucose monitoring (RT-CGM) in adults with T1DM appears to be the best supported in the literature and there is some suggestion that the effects of RT-CGM may be amplified in those patients using an insulin pump. The evidence for CGM in children and adolescents or adults with T2DM is mixed. There is low certainty and conflicting evidence on the use of CGM in pregnant patients, though recent NICE guidance provides for its use in certain circumstances. It should be noted that the primary effectiveness outcome reported in these trials is change in HbA1c. Additionally, while the effect of CGM on HbA1c in the meta-analyses may be statistically significant, the magnitude of the effect appears to be small (invariably <0.5%, a commonly accepted threshold for clinical significance).

Coverage Recommendation (Box Language)

Continuous blood glucose monitoring with real-time or retrospective continuous glucose monitoring systems should only be covered for Type 1 diabetes mellitus patients for whom insulin pump management is being considered, initiated, or utilized and who also have one of the following:

- HbA1c levels greater than 8.0% despite compliance with therapy, or
- A history of recurrent hypoglycemia.

Real-time and retrospective continuous glucose monitoring systems should not be covered for Type 2 diabetes mellitus patients.

Scope Statement

Population description	Children, adolescents, and adults with type 1 or type 2 diabetes mellitus (DM) on insulin therapy, including pregnant women *Population scoping notes: None*
Intervention(s)	Continuous blood glucose monitoring (CBGM), either retrospective or real time *Intervention exclusions: None*
Comparator(s)	Self-monitoring blood glucose (SMBG) and/or routine HbA1c monitoring
Outcome(s) (up to five)	**Critical:** Severe morbidity (e.g. microvascular and macrovascular complications), severe hypoglycemia[1] **Important:** Quality-of-life, change in HbA1c, ketoacidosis *Considered but not selected for GRADE table: Myocardial infarction, cerebrovascular accident, amputations, neuropathy, retinopathy, nephropathy (We chose to generalize these into severe morbidity to simplify consideration), diabetes-related hospitalizations, and emergency department visits.*
Key questions	1. What is the evidence of effectiveness of CGM in improving outcomes in people with diabetes? 2. What are the indications for retrospective and for real time CGM? 3. Is there evidence of differential effectiveness of CGM based on: a. Type 1 vs Type 2 DM? b. Insulin pump vs multiple daily insulin injections (MDII)? c. Frequency and duration of CGM? d. Persistently poor glycemic control

Original Evidence Sources

[1] "An event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions." (ADA Workgroup on Hypoglycemia, 2005)

Langendam, M., Luijf, Y. M., Hooft, L., DeVries, J. H., Mudde, A. H., Scholten, R. J. P. M. (2012). Continuous glucose monitoring systems for type 1 diabetes mellitus. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD008101. DOI: 10.1002/14651858.CD008101.pub2. Retrieved from http://summaries.cochrane.org/CD008101/continuous-glucose-monitoring-systems-for-type-1-diabetes-mellitus.

Golden, S. H., Brown, T., Yeh, H. C., Maruthur, N., Ranasinghe, P., … Bass, E. B. (2012). Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. Comparative Effectiveness Review No. 57. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I.) AHRQ Publication No. 12-EHC036-EF. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Scanning Results

1. Blumer, I., Hadar, E., Hadden, D. R., Jovanovic, L., Mestman, J. H., … Yogev, Y. (2013). Diabetes and pregnancy: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism, 98*(11), 4227-49.

Citation 1 is a clinical practice guideline on diabetes and pregnancy from the Endocrine Society. The guideline suggests that CGM be used in pregnancy "in women with overt or gestational diabetes when self-monitored blood glucose levels (or, in the case of the woman with overt diabetes, HbA1C values) are not sufficient to assess glycemic control…" This is a weak recommendation based on low certainty evidence. (NB: The Endocrine Society has adopted GRADE methodology for their CPGs).

2. Floyd. B., Chandra. P., Hall, S., Phillips, C., Alema-Mensah, E., Strayhorn, G., … Umpierrez, G. E. (2012). Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus. *Journal of Diabetes Science and Technology, 6*(5), 1094-1102.

Citation 2 is a systematic review of RCTs comparing CGM with SMBG in patients with T1DM. The pooled effect appears to be a reduction in A1c of 0.3% favoring CGM (effects were similar for both real-time and retrospective CGM). There was no difference in hypoglycemic events. It should be noted that the search dates for this review (1966 to Nov 2009) are subsumed by both the Cochrane and AHRQ reviews that served as the basis of the 2013 coverage guidance.

3. Hayes, Inc. (2015). *Continuous glucose monitoring systems.* Lansdale, PA: Hayes, Inc.

Citation 3 is a Hayes HTA and systematic review published in August 2015. It includes 23 RCTs and 1 randomized cross-over trial published between 2003 and early 2015. The overall conclusion is that "CGM is reasonably safe but there is conflicting evidence concerning efficacy that is difficult to interpret." They offer a B rating for CGM in adults with T1DM who do not achieve target glycemic control with SMBG; a C rating for use of CGM in adults with T2DM; a C rating for CGM in children and adolescents with T1DM who do not achieve target glycemic control with SMBG; a D2 rating for use of CGM in in children and adolescents with T2DM; and a D2 rating for use of CGM in women with pre-gestational or gestational diabetes (B=Some proven benefit, C=Potential but unproven benefit, D2=Insufficient evidence).

4. Moy, F. M., Ray, A., & Buckley, B. S. (2014). Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes. *Cochrane Database of Systematic Reviews*, Issue 4. Retrieve from http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009613.pub2/epdf

Citation 4 is a Cochrane review of techniques for monitoring blood glucose during pregnancy for women with pre-gestational diabetes (type 1 or 2). The systematic review identified 9 RCTs comparing CGM and SMBG. The authors conclude that there is no evidence that one glucose monitoring technique is superior to another in this population and that the overall evidence base is weak.

5. Neu, A., Beyer, P., Burger-Busing, J., Danne, T., Etspuler, J., Heidtmann, B., … Holterhus P. M., German Diabetes Association. (2014). Diagnosis, therapy and control of diabetes mellitus in children and adolescents. *Experimental & Clinical Endocrinology & Diabetes, 122*(7), 425-34.

Citation 5 is not currently available through the OHSU library. I have requested a manuscript through ResearchGate.

6. NICE. (2015). *Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period.* London: NICE. Retrieved from http://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-its-complications-from-preconception-to-the-postnatal-period-51038446021

Citation 6 is a NICE guideline on the management of diabetes in pregnancy. The guideline states that CGM should not be routinely offered to pregnant women with diabetes, but that it may be considered in pregnant women "who have problematic severe hypoglycemia, unstable blood

glucose levels, or to gain information about variability in blood glucose levels." CGM should only be offered by a team "with expertise in its use."

7. Poolsup, N., Suksomboon, N., & Kyaw, A. M. (2013). Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetology and Metabolic Syndrome, 5*, 39.

Citation 7 is a systematic review and meta-analysis of 14 RCTs comparing CGM with SMBG for children with T1DM (10 trials) or adults with T2DM (4 trials). Overall, there was no significant difference between CGM and SMBG in children with T1DM (mean A1c difference of -0.13%), though the subset of trials comparing RT-CGM to SMBG showed a small benefit in favor of CGM (mean A1c difference of -0.18%). In the trials of adults with T2DM, CGM was slightly better than SMBG with a mean A1c difference of -0.31%.

8. Rewers, M. J., Pillay, K., de Beaufort, C., Craig, M. E., Hanas, R., Acerini, C. L., Maahs, D. M., International Society for Pediatric and Adolescent Diabetes. (2014). *Pediatric Diabetes, 15*(Suppl20), 102-114.

Citation 8 is a clinical practice guideline on assessing and monitoring glycemic control in children and adolescents published by the International Society for Pediatric and Adolescent Diabetes. It states that "CGM devices are becoming available that may particularly benefit those with hypoglycemic unawareness, as the devices will alarm when glucose is below a specified range or with rapid rate of fall of glucose."

9. Szypowska, A., Ramotowska, A., Dzygalo, K., & Golicki, D. (2012). Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: systematic review and meta-analysis of randomized trials. *European Journal of Endocrinology, 166*(4), 567-574.

Citation 9 is a systematic review and meta-analysis of 7 RCTs comparing RT-CGM with SMBG in patients with T1DM. The authors conclude that use of RT-CGM results in better glycemic control (mean A1c difference -0.25%). Use of RT-CGM did not appear to result in increased major hypoglycemic events. The authors note that further studies are needed in children.

10. Voormolen, D. N., DeVries, J. H., Evers, I.M., Mol, B. W., & Franx, A. (2013). The efficacy and effectiveness of continuous glucose monitoring during pregnancy: a systematic review. *Obstetrical & Gynecological Survey, 68*(11), 753-63.

Citation 10 is a systematic review of CGM in pregnancy. The authors note that the current evidence is limited to 2 RCTs with conflicting results and that evidence on cost-effectiveness is lacking.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "continuous glucose" and "glucose monitor." Searches of core sources were limited to citations published after 2011.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2010.

Searches for clinical practice guidelines were limited to those published since 2012. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Coronary Artery Calcium Scoring – 2015 Rescanning Summary

Subcommittee: Evidence-based Guidelines Subcommittee (August 2013)

EbGS Recommendation: Consider development of a new coverage guidance to update this topic upon completion of a pending AHRQ report.

Bottom Line: There is little new summary evidence related to the comparative effectiveness, cost-effectiveness or harms related to coronary calcium scoring. The studies that were identified appear to have substantial limitations and would likely not result in a change to the existing HERC coverage guidance. An AHRQ report on non-invasive testing for coronary artery disease that was started in January 2015 will include information on CACS when published.

Coverage Recommendation (Box Language)

Coronary artery calcium scoring (CACS) should not be covered.

Scope Statement

Population description	Asymptomatic adults with coronary heart disease (CHD) risk, adults with acute chest pain with normal EKG and negative cardiac enzymes, adults with chronic stable chest pain *Population scoping notes:* None
Intervention(s)	Coronary artery calcium scoring (CACS) *Intervention exclusions:* None
Comparator(s)	No further risk stratification, other forms of risk stratification (including serial monitoring (EKG, troponins), exercise EKG, stress echocardiography, stress myocardial perfusion scanning, coronary angiography, clinical risk prediction tools
Outcome(s) (up to five)	**Critical:** All-cause mortality, major adverse cardiovascular events **Important:** Incidental findings, avoidance of invasive procedure *Considered but not selected for GRADE table:* Length of stay
Key questions	1. What is the comparative effectiveness of CACS in improving outcomes for asymptomatic patients with CHD risk or patients with chest pain (either acute chest pain with normal EKG and

	negative cardiac enzymes or chronic stable chest pain)? 2. What is the cost-effectiveness of CACS? 3. What are the harms of CACS?
Contextual questions	1. Does CACS alter treatment plans by refining estimates of risk?

Original Evidence Sources

Hayes, Inc. (2012). *Coronary artery calcium scoring to assess the risk of coronary artery disease in asymptomatic adults.* Lansdale, PA: Hayes, Inc.

National Institute for Health and Clinical Excellence (NICE). (2010). *Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin.* London: NICE. Retrieved August 31, 2012 from http://www.nice.org.uk/nicemedia/live/12947/47938/47938.pdf

U.S. Preventive Services Task Force. (2009). Using nontraditional risk factors in coronary heart disease risk assessment 2009. Retrieved August 31, 2012 from http://www.uspreventiveservicestaskforce.org/uspstf09/riskcoronaryhd/coronaryhdrs.htm

Washington State Health Care Authority Health Technology Assessment Program. (2009). *Coronary artery calcium scoring (CACS) as a diagnostic test for detection of coronary artery disease.* Olympia, WA: Health Technology Assessment Program. Retrieved August 31, 2012 from http://www.hta.hca.wa.gov/calscoring.html

Scanning Results (reviewed for applicability, methodologic quality not assessed)

1. Fihn, S. D., Gardin, J. M., Abrams, J., Berra, K., Blankenship, J. C., Dallas, A. P., … Williams, S. V. (2012). 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. *Circulation, 126*, e354-e471. DOI: 10.1161/CIR.0b013e318277d6a0

2. Kramer, C. K., Zinman, B., Gross, J. L., Canani, L. H., Rodrigues, T. C., Azevedo, M. J., & Retnakaran, R. (2013). Coronary artery calcium score prediction of all cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. *British Medical Journal, 346*, f1654. DOI: 10.1136/bmj.f1654

3. Mammen, L., Abbara, S., Dorbala, S., Javidan-Nejad, C., Julsrud, P. R., Kirsch, J., …Woodard, P. K., Expert Panel on Cardiac Imaging. (2014). *ACR Appropriateness Criteria® chest pain suggestive of acute coronary syndrome*. Reston, VA: American College of Radiology. Retrieved August 3, 2015 from http://www.acr.org/~/media/dac4a22870304676809355ebc2a9ab47.pdf

4. Raman, V., McWilliams, E. T., Holmberg, S. R., & Miles, K. (2012). Economic analysis of the use of coronary calcium scoring as an alternative to stress ECG in the non-invasive diagnosis of coronary artery disease. *European Radiology, 22*(3), 579-587. DOI 10.1007/s00330-011-2304-2

5. Woodard, P. K., White, R. D., Abbara, S., Araoz, P. A., Cury, R. C., Dorbala, S., … White, C. S., Expert Panel on Cardiac Imaging. (2012). *ACR Appropriateness Criteria® chronic chest pain - low to intermediate probability of coronary artery disease*. Reston, VA: American College of Radiology. Retrieved August 3, 2015 from https://acsearch.acr.org/docs/69337/Narrative/

6. Xie, X., Zhao, Y., de Bock, G. H., de Jong, P. A., Mali, W. P., Oudkerk, M., & Vliegenthart, R. (2013). Validation and prognosis of coronary artery calcium scoring in nontriggered thoracic computed tomography: systematic review and meta-analysis. *Circulation: Cardiovascular Imaging, 6*(4), 514-521. DOI: 10.1161/CIRCIMAGING.113.000092

Summary:

Citation 1 is a joint clinical practice guideline from seven professional societies. The guideline states that coronary artery calcium scoring may be considered for patients who have a low to intermediate pre-test probability of obstructive ischemic heart disease. The recommendation is based on consensus opinion, case studies and/or the determined standard of care.

Citation 2 is a systematic review of eight studies (n=6,521) that focuses on the use of coronary artery calcium scoring for reducing all-cause mortality and cardiovascular events in patients with type 2 diabetes. The overall reported sensitivity and sensitivity of a calcium score $\geq$ 10 were 94% and 34%, respectively, for detecting all-cause mortality and cardiovascular events at a mean follow-up interval of 5 years. This corresponds to a positive likelihood ratio of 1.67 and a negative likelihood ratio of 0.11. The clinical significance of testing in this population (i.e. whether it influences management decisions or alters clinical outcomes) remains unclear.

Citation 3 is a clinical practice guideline that states CT coronary calcium is usually not appropriate for diagnosing chest pain suggestive of acute coronary syndrome and is not validated in the acute setting. The guideline notes that CT coronary calcium has a medium level of relative radiation (1-10 mSv for adults).

Citation 4 is an economic analysis comparing coronary artery calcium scoring with stress electrocardiography. The analysis was based on national prices in the United Kingdom and may be too indirect to influence the HERC coverage guidance.

Citation 5 is a clinical practice guideline that states CT coronary calcium is usually not appropriate for diagnosing chronic chest pain in patients with a low to intermediate pre-test probability of coronary artery disease. The guideline notes that CT coronary calcium has a medium level of relative radiation (1-10 mSv for adults).

Citation 6 is a systematic review and meta-analysis of five studies (n=34,028) evaluating the prognostic performance of coronary artery calcium scoring in asymptomatic patients. Of note, the main data sources are studies of chest CT for lung cancer screening and the highly heterogeneous results in the prognostic studies precluded meta-analysis. The study did not evaluate whether using calcium scoring resulted in a change of care or prevented any major adverse cardiac events or death.

Note: The Agency for Healthcare Research and Quality Effective Health Care Program is currently in the process of reviewing noninvasive testing for coronary artery disease. The protocol was initiated in January 2015.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "calcium scor*," "computed tomography coronary," "computed tomography calcium," and "cardiac CT." Searches of core sources were limited to citations published after 2011 (the last search date of original evidence sources).

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2011 (the last search date of the original evidence sources).

Searches for clinical practice guidelines were limited to those published since 2012 (last search date of coverage guidance). A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, , did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Coronary Computed Tomography Angiography – 2015 Rescanning Summary

Subcommittee: Evidence-based Guidelines Subcommittee (August 2013)

EbGS Recommendation: Consider development of a new coverage guidance to update this topic upon completion of a pending AHRQ report.

Bottom Line: New summary evidence and clinical practice guidelines pertaining to the use of CCTA are now available. Most of the new data further establishes the diagnostic performance (but not clinical utility) of CCTA, though there is some tentative data on downstream testing utilization and clinical outcomes. An AHRQ report on non-invasive testing for coronary artery disease that was started in January 2015 will include information on CCTA when published.

Coverage Recommendation (Box Language)

Coronary computed tomography angiography (CCTA) is not recommended for coverage.

Scope Statement

Population description	Adults with acute chest pain or chronic stable chest pain *Population scoping notes:* None
Intervention(s)	Coronary CT angiography (CTA) *Intervention exclusions:* None
Comparator(s)	Usual care (including no additional testing, exercise EKG, stress echocardiography, stress myocardial perfusion scanning, coronary angiography; serial monitoring with EKG/troponin)
Outcome(s) (up to five)	**Critical:** All-cause mortality, major adverse cardiac events (MACE) **Important:** Contrast-induced nephropathy, avoidance of invasive procedures *Considered but not selected for GRADE table:* radiation exposure; need for revascularization procedure
Key questions	1. What is the comparative effectiveness of coronary CTA for improving outcomes among adults with chest pain?

	a. Are there patient characteristics that modify the utility? 2. What are the harms of coronary CTA (including incidental findings)? 3. What are the comparative costs and/or cost-effectiveness of coronary CTA?

Original Evidence Sources

Clark, E.E. (2011). *Coronary computed tomographic angiography*. Portland: Center for Evidence-based Policy. Retrieved August 31, 2012 from http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policycenter/med/index.cfm

Institute for Clinical and Economic Review. (2012). *Update on coronary ct angiography: New clinical trial evidence*. Boston: Institute for Clinical and Economic Review. Retrieved September 18, 2012 from http://www.icerreview.org/index.php/Completed-Appraisals/ccta.html

National Institute for Health and Clinical Excellence (NICE). (2010*). Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin*. London: NICE. Retrieved August 31, 2012 from http://publications.nice.org.uk/chest-pain-of-recent-onset-cg95

Ollendorf, D.A. (2009). *Coronary computed tomographic angiography for the detection of coronary artery disease*. Boston: Institute for Clinical and Economic Review. Retrieved September 18, 2012 from http://www.icer-review.org/index.php/Completed-Appraisals/ccta.html

Scanning Results (reviewed for applicability, methodologic quality not assessed)

1. Ayaram, D., Bellolio, M. F., Murad, M. H., Laack, T. A., Sadosty, A. T., Erwin, P. J., … Hess, E. P. (2013). Triple rule-out computed tomographic angiography for chest pain: a diagnostic systematic review and meta-analysis. *Academic Emergency Medicine, 20*(9), 861-871. DOI: 10.1111/acem.12210

2. Canadian Agency for Drugs and Technologies in Health (CADTH). (2014). *Diagnostic computed tomography angiography for adult patients: Safety.* Ontario, Canada: CADTH. Retrieved

July 27, 2015 from https://www.cadth.ca/sites/default/files/pdf/htis/mar-2014/RB0660%20CTA%20Safety%20final.pdf

3. D'Ascenzo, F., Cerrato, E., Biondi-Zoccai, G., Omede, P., Sciuto, F., Presutti, D. G., … Gaita, F. (2013). Coronary computed tomographic angiography for detection of coronary artery disease in patients presenting to the emergency department with chest pain: a meta-analysis of randomized clinical trials. *European Heart Journal – Cardiovascular Imaging, 14*(8), 782-789. DOI:10.1093/ehjci/jes287

4. Darlington, M., Gueret, P., Laissy, J. P., Pierucci, A. F., Maoulida, H., Quelen, C., … Durand-Zaleski, I. (2014). Cost-effectiveness of computed tomography coronary angiography versus conventional invasive coronary angiography. *European Journal of Health Economics, 16*(6), 647-655. DOI 10.1007/s10198-014-0616-2

5. Davis, T., Bluhm, J., Burke, R., Iqbal, Q., Kim, K., Kokoszka, M., … Zwank, M. (2012). *Diagnosis and treatment of chest pain and acute coronary syndrome (ACS*). Bloomington (MN): Institute for Clinical Systems Improvement. Retrieved July 28, 2015 from https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_cardiovascular_guidelines/acute_coronary_syndrome/

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Summary

Citation 1 is a SR and MA of studies examining the use of CTA for the so-called triple rule-out (CAD, PE, dissection) of adults with chest pain in the emergency department. It concludes that CTA is highly accurate for detecting CAD, but that the low prevalence of PE and dissection in the studies provide insufficient data to support the triple-rule out. The meta-analytic information presented on the operating characteristics of CTA for CAD in this selected population would potentially change HERC coverage guidance.

Citation 2 is a CADTH rapid response that summarizes two non-randomized studies on the risk of contrast-induced renal injury from CTA.

Citation 3 is a SR and MA of 4 RCTs examining the use of CCTA in ED patients with chest pain. The main outcomes reported were odds of undergoing a revascularization procedure, time to diagnosis, and costs of ED care. It would potentially change HERC coverage guidance.

Citation 4 is a cost-effectiveness study of CCTA vs conventional angiography using a micro-costing method in 4 French hospitals. Any conclusions are probably too indirect to influence the HERC coverage guidance.

Citation 6 is a SR and MA examining how the operating characteristics of CCTA are affected by the presence of coronary artery calcification detected by CACS and/or the use of 64-slice vs 16-slice MDCT technology. It might provide contextual information if the HERC coverage guidance is updated.

Citation 7 is an AHRQ comparative effectiveness review on the non-invasive diagnosis of CAD in women. It concludes that evidence of low strength supports the diagnostic accuracy of CCTA, but there is insufficient evidence that it improves risk stratification, decision making, or clinical outcomes.

Citation 8 is a SR and MA of CCTA vs standard care for evaluation of low-risk chest pain. It includes data from 4 RCTs and 3 case-control studies and concludes that the use of CCTA is associated with decreased risk of ACS and fewer repeat ED visits. It would potentially change HERC coverage guidance.

Citation 9 is the 2012 ACCF/AHA/et al guideline on the diagnosis and management of stable ischemic heart disease (SIHD). The recommendations concerning CCTA in patients with suspected or known SIHD who require non-invasive testing are all class IIa (is reasonable) or IIb (may be considered) with a levels of evidence B-C. These guidelines would potentially change HERC coverage guidance.

Citation 10 is a decision analytic study comparing the effectiveness and costs of CCTA vs stress EKG based on information from a single prospective cohort of 471 patients. The economic evaluation made assumptions based on the Dutch Health Care Insurance board. The design of the study and the indirectness of the information on cost make it unlikely to influence HERC coverage guidance.

Citation 11 is cost-effectiveness study comparing 64-slice CCTA with conventional angiography. It would probably provide contextual information on resource use if the topic is selected for updating.

Citation 12 is a SR and MA of non-comparative studies that report >3 months of clinical follow-up for patients undergoing 64-slice CCTA. The report provides OR for cardiac death or MI based on the findings of the CCTA. Obstructive and non-obstructive CAD on CCTA had higher OR for the outcomes compared to those without CAD.

Citation 13 is a randomized controlled trial of 1000 patients between the ages of 40-74 years presenting to the ED with symptoms of ACS but without EKG or biochemical evidence of ischemia; they were randomly assigned to either CCTA or standard evaluation. The CCTA strategy resulted in shortened time to diagnosis and length of hospital stay, but the overall cost of care was not significantly different in the two groups. It may provide contextual information about the incorporation of CCTA into clinical workflows if the topic is selected for updating.

Citation 14 is a SR and MA of 4 RCTs comparing CCTA and usual care for patients in the ED with chest pain. It concludes that CCTA use decreased ED costs and length of stay, but increased invasive coronary angiography and revascularization.

Citation 15 is the ACR Appropriateness Criteria for patients with acute chest pain and suspected aortic dissection. It recommends CTA of the chest and abdomen as the definitive test in most patients with suspicion of aortic dissection. This recommendations does not specifically apply to coronary CTA, and thus would be unlikely to change the HERC coverage guidance.

Citation 16 is a SR and MA of non-comparative studies of patients with suspected coronary disease who underwent CCTA with follow-up of at least 12 months. The primary outcomes were test characteristics for predicting MACE. The weighted average annualized MACE rate was 3.49% for patient with “positive” CCTA and 0.21% for patients with “negative” CCTA. It is not clear that information from this study would change HERC coverage guidance.

Citation 17 is a study of CCTA for detecting graft vasculopathy in patients who have had a heart transplant and is thus out of scope.

Citation 18 is a SR and MA of 10 studies examining the diagnostic accuracy of 320-slice CCTA. It provides information on the incremental diagnostic accuracy of more advanced CT technology.

Citation 19 is a SR and MA of studies comparing the diagnostic performance of 64-slice MDCT and post 64-slice MDCT with coronary angiography. It provides information on the comparative diagnostic performance of two CCTA technologies.

Citation 20 is an economic evaluation of CCTA in the Italian health care system. Any conclusions are probably too indirect to influence the HERC coverage guidance.

Citation 21 is the ACR Appropriateness Criteria for patients with symptoms suggestive of acute coronary syndrome. It suggests that CCTA can be considered for “those patients with low-to-

intermediate likelihood for coronary artery disease in the absence of cardiac enzyme elevation and ischemic ST changes.

Citation 22 is a small (180 patients) prospective multicenter RCT comparing CCTA and myocardial perfusion imaging (MPI) as the initial diagnostic evaluation for patients with stable chest pain and suspected CAD. It concludes that CCTA and MPI show comparable improvements in angina-related QoL. CCTA is associated with more aggressive medical therapy and increased revascularization, but lower total costs and effective radiation dose. It is a small but reasonably well done RCT that could potentially inform HERC coverage guidance.

Citation 23 is a narrative review of evidence and cost-effectiveness data on CCTA in patients with chronic chest pain. It provides a critical review of some of the general limitations of the literature and would provide important contextual information if the topic is selected to be updated.

Citation 24 is a single center retrospective cohort study comparing patients who received CCTA or exercise stress testing in symptomatic patients with low-to-intermediate pretest probability of CAD. It provides clinical and cost outcomes at 12 months of follow-up for these patients. The design makes it unlikely that this study would change the HERC coverage guidance.

Citation 25 is a SR and MA of studies comparing the diagnostic accuracy and clinical outcomes of exercise EKG and SPECT vs CCTA in patients with suspected stable CAD. It concludes that the diagnostic performance of CCTA is better than exercise EKG or SPECT and that CCTA is associated with lower odds of non-fatal MI and increased downstream testing and coronary revascularization. It would be potentially change the HERC coverage guidance.

Citation 26 is a SR of prospective non-randomized controlled trials and diagnostic accuracy studies of 64-slice CT and coronary angiography. It concludes that 64-slice CT is highly sensitive and specific for the diagnosis of significant coronary stenosis in patients with angina. The authors propose that CCTA should replace angiography as the gold-standard diagnostic test for CAD. It would potentially change HERC coverage guidance.

Citation 27 is a multisociety (ACP/ACCF/AHA/et al) guideline on the diagnosis of stable ischemic heart disease. Pertinent recommendations include a) that CCTA should not be used for risk assessment in patients with stable IHD who are able to exercise and have an interpretable EKG, b) that CCTA should not be used in conjunction with other tests to assess risk in patients with stable IHD. However, CCTA is included in the testing algorithm for ischemic heart disease and would therefore potentially change the HERC coverage guidance.

Citation 28 is an economic analysis of coronary artery calcium scoring compared with stress EKG for the non-invasive diagnosis of CAD. It is therefore out of scope.

Citation 29 is a SR and MA of diagnostic accuracy studies of dual-source CT for CAD. The included studies were published between 2005 and 2011 and would likely have been captured in the summary evidence sources used for the 2013 coverage guidance.

Citation 30 is SR and MA of studies of CCTA for diagnosis of chest pain for patients in the ED with suspected ACS. It concludes that CCTA has high sensitivity and a low negative LR and is therefore effective in ruling out ACS in low-to-intermediate risk ED patients with acute chest pain.

Citation 31 is a SR and MA of studies examining the diagnostic performance of EKG-gated CCTA for the diagnosis of CAD. It concludes that EKG-gated CCTA has favorable diagnostic performance with pooled sensitivity and specificity of 99% and 91% respectively.

Citation 32 is a SR and MA of studies examining the diagnostic performance of combined use of CCTA and computed tomographic perfusion (CTP) for diagnosis of significant coronary stenosis. It is therefore out of scope.

Citation 33 is a SR and MA of dual-source CCTA for the diagnosis of CAD in "difficult to image patients." It concludes that dual-source CCTA "may be sufficiently accurate to diagnose clinically significant CAD in some or all difficult to image patients." It could potentially change HERC coverage guidance.

Citation 34 is a SR and MA of studies of CCTA in graft vasculopathy following cardiac transplantation. It is therefore out of scope.

Citation 35 is the ACR Appropriateness Criteria for patients with chronic chest pain and low-to-intermediate probability of CAD. It recommends that CCTA "can be used to assess for coronary atherosclerosis, anomalous coronary artery, and pericardial disease. High negative predictive value will exclude coronary artery disease and allow triage management to focus on more likely diagnoses." It could potentially change HERC coverage guidance.

Citation 36 is SR of 42 studies examining the comparative effectiveness, cost-effectiveness, and effects on downstream test utilization of CCTA. It concludes that CCTA may be a cost-effective strategy and reduce downstream testing in stable chest pain patients with low-to-intermediate risk. It could potentially change HERC coverage guidance.

Note: The Agency for Healthcare Research and Quality Effective Health Care Program is currently in the process of reviewing noninvasive testing for coronary artery disease. The protocol was initiated in January 2015.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "coronary computed tomography" and "coronary CT angiography." Searches of core sources were limited to citations published after 2011 (last search date of original evidence sources).

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2011(last search date of the original evidence sources).

Searches for clinical practice guidelines were limited to those published since 2012 (last search date of coverage guidance). A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, , did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Diagnosis of Obstructive Sleep Apnea – 2015 Rescanning Summary

Subcommittee: Health Technology Assessment Subcommittee (HERC approved May 2013)

HTAS Recommendation: Develop a new coverage guidance to update this topic.

Bottom Line: Most of the newly available evidence pertains to the comparability of portable level III testing with the gold standard level I testing that is done in a sleep lab. Portable level III testing appears to have favorable diagnostic performance in adults with a high pre-test probability of uncomplicated OSA and may be less expensive. While the additional evidence identified in this search would be unlikely to substantially alter the existing coverage guidance, HERC may wish to consider addressing clinical pathways to encourage the most efficient use of less costly diagnostic tests or empiric therapeutic trials in selected patients with a high pre-test probability of uncomplicated sleep apnea.

Coverage Recommendation (Box Language)

The following diagnostic tests for Obstructive Sleep Apnea (OSA) should be covered for adults:

1. Type I PSG is covered when used to aid the diagnosis of OSA in patients who have clinical signs and symptoms indicative of OSA if performed attended in a sleep lab facility.

2. Type II or Type III sleep testing devices are covered when used to aid the diagnosis of OSA in patients who have clinical signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.

3. Type IV sleep testing devices measuring three or more channels, one of which is airflow, are covered when used to aid the diagnosis of OSA in patients who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.

4. Sleep testing devices measuring three or more channels that include actigraphy, oximetry, and peripheral arterial tone, are covered when used to aid the diagnosis of OSA in patients who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.

Scope Statement

Population description	Adults with clinical signs and symptoms of obstructive sleep apnea (OSA) *Population scoping notes: None*
Intervention(s)	Polysomnography; attended or unattended, sleep lab or at home *Intervention exclusions: None*
Comparator(s)	Usual care
Outcome(s) (up to five)	Critical: Major adverse cardiovascular events, fatigue-related accidents Important: Improvement in HTN, measures of daytime fatigue, quality-of-life *Considered but not selected for GRADE table: Resolution of metabolic syndrome*
Key questions	1. What is the effectiveness of polysomnography in improving outcomes for patients with suspected OSA? a. What are the diagnostic cutoffs associated with improved outcomes? 2. What is the differential effectiveness of polysomnography based on the type of device used or the setting in which testing is performed? 3. What are the harms of polysomnography? Contextual Questions 1. Are there clinically validated tools (i.e. questionnaires and/or physical parameters) to assess the pre-test probability of OSA? a. If validated tools exist, at what levels of pretest probability should polysomnography not be recommended? 2. Are there evidence-based clinical pathways to promote efficient use of diagnostic testing or empiric therapeutic trials in selected patients?

Original Evidence Source

Gleitsmann, K., Kriz, H., Thielke, A., Bunker, K., Ryan, K., Lorish, K., & King, V. (2012). *Sleep apnea diagnosis and treatment in adults.* Produced for the Washington HTA Program. Olympia, WA: Center for Evidence-based Policy, Oregon Health and Science University for the Washington Health Technology Assessment Program. Retrieved from http://www.hta.hca.wa.gov/documents/sleep_apnea_final_report.pdf .

Scanning Results

1. Alberta Technology & Policy Unit. (2013). *Level I and level III sleep studies for the diagnosis of Sleep Disordered Breathing (SDB) in adults*. Edmonton: Health Technology & Policy Unit (HTPU).

Citation 1 is an Alberta Health Technology and Policy Unit report on the use of level I and level III sleep studies for the diagnosis of sleep disordered breathing. The authors conclude that level I sleep studies are the reference standard for diagnosis of sleep disordered breathing. They further conclude that level III (in-home) sleep studies are appropriate when there is a high pre-test probability of uncomplicated moderate-severe obstructive sleep apnea.

2. Andreu, A. L., Chiner, E., Sancho-Chust, J. N., Pastor, E., Llombart, M., Gomez-Merino, E., … Barbe, F. (2012). Effect of an ambulatory diagnostic and treatment programme in patients with sleep apnoea. *European Respiratory Journal, 39*(2), 305-312.

Citation 2 is a RCT comparing three testing strategies for diagnosis of OSA. The authors conclude that in patients with a high pre-test probability of OSA that home testing is effective and less costly then testing in a sleep lab and that adherence to CPAP therapy is similar. The study was done in Spain and the economic analysis may be too indirect to apply to this coverage guidance.

3. El Shayeb, M., Topfer, L. A., Stafinski, T., Pawluk, L., & Menon, D. (2014). Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: a systematic review and meta-analysis. *CMAJ: Canadian Medical Association Journal*, 186(1), E25-E51.

Citation 3 is a SR and MA of 19 studies comparing level 1 and level 3 polysomnography for the diagnosis of sleep disordered breathing. The authors conclude that for adults with a high pre-test probability of OSA, level 3 and level 1 sleep studies have comparable diagnostic performance. For other types of sleep disordered breathing (i.e. non-OSA), level 1 testing is still recommended.

4. Fedson, A. C., Pack, A. I., & Gislason, T. (2012). Frequently used sleep questionnaires in epidemiological and genetic research for obstructive sleep apnea: a review. *Sleep Medicine Reviews, 16*(6), 529-37.

Citation 4 is a review of sleep apnea questionnaires as they apply to epidemiological and genetic studies of sleep apnea. The authors conclude that improved standardized instruments are needed.

5. Friedman, M., Hamilton, C., Samuelson, C. G., Lundgren, M. E., & Pott, T. (2013). Diagnostic value of the Friedman tongue position and Mallampati classification for obstructive sleep apnea: a meta-analysis. *Otolaryngology - Head and Neck Surgery, 148*(4), 540-547

Citation 5 is a SR of studies of the Friedman tongue position or Mallampati class to predict the severity of OSA. The authors conclude that these assessments of oral anatomy can help predict OSA severity.

6. Hayes, Inc. (2014). *Apnea Risk Evaluation System (ARES; Watermark Medical Inc.) for diagnosis of obstructive sleep apnea*. Lansdale, PA: HAYES, Inc.

Citation 6 is a Hayes review of a proprietary portable system for the diagnosis of OSA (ARES). The authors conclude that data from a mix of cohort and case-control studies provide insufficient evidence of efficacy for the ARES device.

7. Myers, K. A., Mrkobrada, M., & Simel, D. L. (2013). Does this patient have obstructive sleep apnea?: The Rational Clinical Examination systematic review. *JAMA, 310*(7), 731-41.

Citation 7 is a JAMA Rationale Clinical Exam article that includes a SR of the likelihood ratios of various signs or symptoms of sleep apnea.

8. Nishiyama, T., Mizuno, T., Kojima, M., Suzuki, S., Kitajima, T., Ando, K. B., … Nakayama, M. (2014). Criterion validity of the Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale for the diagnosis of sleep disorders. *Sleep Medicine, 15*(4), 422-429.

Citation 8 is a single-center Japanese study examining the criterion validity of two questionnaires for the diagnosis of 4 sleep disorders (including OSA). The authors conclude that that the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale. The authors conclude that these scales should not be used for screening or diagnosis of sleep disorders.

9. Qaseem, A., Dallas, P., Owens, D. K., Starkey, M., Holty, J. E., Shekelle, P., Clinical Guidelines Committee of the American College of Physicians. (2014). Diagnosis of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine, 161*(3), 210-20.

Citation 9 is a clinical practice guideline from the American College of Physicians. It offers the following recommendations:

1. ACP recommends a sleep study for patients with unexplained daytime sleepiness. (Grade: weak recommendation, low-quality evidence)
2. ACP recommends polysomnography for diagnostic testing in patients suspected of obstructive sleep apnea. ACP recommends portable sleep monitors in patients without serious comorbidities as an alternative to polysomnography when polysomnography is not available for diagnostic testing. (Grade: weak recommendation, moderate-quality evidence)

10. Trakada, G., Economou, N. T., Nena, E., Trakada, A., Zarogoulidis, P., & Steiropoulos, P. (2015). A health-economic analysis of diagnosis and treatment of obstructive sleep apnea with continuous positive airway pressure in relation to cardiovascular disease. The Greek experience. *Sleep and Breathing*, *19*(2), 467-72.

Citation 10 is a health economic analysis regarding the diagnosis and treatment of sleep apnea in Greece. It would likely be too indirect to inform a new coverage guidance.

11. Yalamanchali, S., Farajian, V., Hamilton, C., Pott, T. R., Samuelson, C. G., & Friedman, M. (2013). Diagnosis of obstructive sleep apnea by peripheral arterial tonometry: meta-analysis. *JAMA Otolaryngology - Head and Neck Surgery, 139*(12), 1343-1350.

Citation 11 is a meta-analysis comparing peripheral arterial tonometry (PAT) to polysomnography for the diagnosis of sleep apnea. The authors conclude that PAT-based portable devices are an acceptable alternative to polysomnography for the diagnosis of OSA.

12. Zancanella, E. Haddad, F. M. Oliveira, L. A., Nakasato, A., Duarte, B. B., Soares, C. F., … Andrada, N. C., Associacao Brasileira de Otorrinolaringologia e Cirurgia Cervico-Facial, Academia Brasileira de Neurologia, Sociedade Brasileira de Cardiologia, Sociedade Brasileira de Pediatria, & Sociedade Brasileira de Pneumologia e Tisiologia. (2014). Obstructive sleep apnea and primary snoring: diagnosis. *Revista Brasileira de Otorrinolaringologia, 80*(1 Suppl 1), S1-16.

Citation 12 is a clinical practice guideline from the Brazilian Association of Otolaryngology and Neck and Facial Surgery. The recommendation for testing for OSA is:
Monitored full-night PSG performed in a sleep laboratory is considered the gold standard for OSAS diagnosis (B). The diagnostic probability is similar when performing PSG
I and II... Portable sleep monitoring assessments still have the limitation of monitoring channel loss due to failure, or loosening or disconnection of sensors (D), and the need to perform a new PSG I or II to rule out false negatives in cases of high disease probability and normal initial monitoring results (D).

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "polysomnography," "apnea diagnosis," and "sleep diagnos*." Searches of core sources were limited to citations published after 2011.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2011.

Searches for clinical practice guidelines were limited to those published since 2012. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Induction of Labor – 2015 Rescanning Summary

Subcommittee: Evidence-based Guidelines Subcommittee (HERC approved August 2013)

EbGS Recommendation: Reaffirm the existing coverage guidance and reconsider the need to update it during the regular two-year review cycle.

Bottom Line: There is little new evidence related to the benefits or harms of induction of labor (IOL). The studies that were identified would not likely result in a change to the HERC coverage guidance issued in 2013.

Coverage Recommendation (Box Language)

Induction of labor is recommended for coverage for the following indications *(strong recommendation)*:

- Gestational age beyond 41 weeks 0 days
- Prelabor rupture of membranes, term
- Fetal demise
- Preeclampsia, term (severe or mild)
- Eclampsia
- Chorioamnionitis

Induction of labor is recommended for coverage for the following indications *(weak recommendation)*:

- Diabetes, pre-existing and gestational
- Placental abruption
- Preeclampsia, preterm (severe or mild)
- Severe preeclampsia, preterm
- Cholestasis of pregnancy
- Preterm, prelabor rupture of membranes;
- Gastroschisis
- Twin gestation
- Maternal medical conditions (e.g., renal disease, chronic pulmonary disease, chronic hypertension, cardiac disease, antiphospholipid syndrome)
- Gestational hypertension
- Fetal compromise (e.g., isoimmunization, oligohydramnios)
- Intrauterine growth restriction/Small for gestational age, term

- Elective purposes, >39 weeks 0 days to <41 weeks 0 days (without a medical or obstetrical indication) with a favorable cervix (for example, with a Bishop score ≥6)

Induction of labor is not recommended for coverage for the following indications *(weak recommendation):*

- Macrosomia (in the absence of maternal diabetes)
- Elective purposes, >39 weeks 0 days to <41 weeks 0 days (without a medical or obstetrical indication) with an unfavorable cervix (for example, a Bishop score <6)
- Intrauterine growth restriction/Small for gestational age, preterm (without other evidence of fetal compromise)

Induction of labor is not recommended for coverage for the following indications *(strong recommendation):*

- Elective purposes <39 weeks (without a medical or obstetrical indication)

Scope Statement

Population description	Pregnant adolescents and women *Population scoping notes: None*
Intervention(s)	IOL without medical or obstetrical indications *Intervention exclusions: None*
Comparator(s)	Expectant management
Outcome(s) (up to five)	**Critical:** Perinatal mortality, maternal mortality, neonatal morbidity **Important:** Mode of birth (stratified by indication for operative delivery), maternal length of stay *Considered but not selected for GRADE table: Iatrogenic prematurity, hemorrhage, epidural, patient satisfaction, neonatal length of stay*
Key questions	1. What are the outcomes of IOL versus expectant management for women without medical or obstetrical indications for induction of labor? 2. How do outcomes vary by cervical favorability, gestational age and parity?

Contextual question	1. What are the evidence-based medical or obstetrical indications for induction of labor?

Original Evidence Sources

American College of Obstetrics and Gynecology (ACOG). (2009). Induction of labor. ACOG Practice Bulletin No. 107, American College of Obstetricians and Gynecologists. *Obstetrics & Gynecology*, *114*, 386-97. Guideline summary available at: http://www.guidelines.gov/content.aspx?id=14884

King, V., Pilliod, R., & Little, A. (2010). *Rapid review: Elective induction of labor*. Portland: Center for Evidence-based Policy. Retrieved from http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policycenter/med/index.cfm

Mozurkewich, E., Chilimigras, J., Koepke, E., Keeton, K., & King, V. J. (2009). Indications for induction of labour: a best-evidence review. *British Journal of Obstetrics and Gynecology, 116*, 626-636. DOI: 10.1111/j.1471-0528.2008.02065.x.

National Institute for Health and Clinical Excellence (NICE), & National Collaborating Centre for Women's and Children's Health. (2008). Induction of labour. London: RCOG Press at the Royal College of Obstetricians and Gynaecologists. Retrieved from http://guidance.nice.org.uk/CG70/Guidance/pdf/English

Scanning Results

1. Dodd, J. M., Crowther, C. A., Grivell, R. M., & Deussen, A. R. (2014). Elective repeat caesarean section versus induction of labour for women with a previous caesarean birth. *Cochrane Database of Systematic Reviews,* Issue 12. Art. DOI: 10.1002/14651858.CD004906.pub4.

Citation 1 identified no RCTs available to inform management of this population.

2. Dodd, J. M., Deussen, A. R., Grivell, R. M., & Crowther, C. A. (2014). Elective birth at 37 weeks' gestation for women with an uncomplicated twin pregnancy. *Cochrane Database of Systematic Reviews*, Issue 2. Art. DOI: 10.1002/14651858.CD003582.pub2.

Citation 2 identified no new studies since its prior update and had no changes in conclusions. Elective birth at 37 weeks increased the risk of infants being born at less than the third centile of birthweight compared with expectant management, but there were no other significant

differences in maternal or fetal/neonatal outcomes. Current HERC guidance provides a weak recommendation for IOL for twin gestations, but does not specify gestational age restrictions.

3. Gülmezoglu, A. M., Crowther, C. A., Middleton. P/, & Heatley, E. (2012). Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database of Systematic Reviews*, Issue 6. Art. DOI: 10.1002/14651858.CD004945.pub3.

The findings of Citation 3 do not change the conclusions of the HERC guidance. Perinatal deaths were lower with IOL at >41 weeks of gestation, but were not significantly different at fewer weeks of gestation. There were fewer cases of meconium aspiration syndrome and macrosomia at 41 and >41 weeks with IOL, but no differences in NICU admission or Apgar score <7 at 5 minutes. Cesarean births were lower with IOL at 41 and >41 weeks, but not significantly different at 37 to 40 weeks of gestation. Operative vaginal births (forceps or vacuum) were more frequent at 37 to 39 weeks with IOL, but not at higher gestational ages. This SR/MA found higher rates of Cesarean birth with "unfavorable" (as defined by study authors, but commonly Bishop Score >6) cervical status, but did not simultaneously control for gestational age or other risk factors.

4. Kaimal, A. J., Little, S. E., Odibo, A. O., Stamilio, D. M., Grobman, W. A., Long, E. F., … Caughey, A. B. (2011). Cost-effectiveness of elective induction of labor at 41 weeks in nulliparous women. *American Journal of Obstetrics and Gynecology, 204*(2), 137.e1-137.e9. DOI: http://dx.doi.org/10.1016/j.ajog.2010.08.012.

Citation 4 is a cost-effectiveness study of eIOL vs. expectant management using a decision-analytic model. Modeling was used rather than a primary economic study done alongside a RCT or other type of study and therefore is subject to the associated usual biases of modeling studies. The analysis found that eIOL at 41 weeks was cost-effective with an incremental cost of $10, 945 per QALY. The authors stated that improved outcomes, including neonatal mortality/morbidity and fewer maternal severe perineal lacerations helped to account for the incremental cost difference.

5. Hussain, A. A., Yakoob, M. Y., Imdad, A., & Bhutta, Z. A. (2011). Elective induction for pregnancies at or beyond 41 weeks of gestation and its impact on stillbirths: a systematic review with meta-analysis. *BMC Public Health, 11*(Supplement 3), S5. DOI: 10.1186/1471-2458-11-S3-S5.

Citation 5 is a SR/MA of eIOL vs. expectant management for pregnancies ≥ 41 weeks of gestation. The SR included 25 studies, of all study designs, and the primary outcome of interest was stillbirth. The authors concluded that eIOL decreases perinatal death overall (RR 0.31, 95%

CI 0.11-0.88), but not stillbirth (RR 0.29, 95% CI 0.06-1.38). These findings are in line with evidence considered for the current HERC guidance.

6. Kenny, T. H., Nicodemo, J. M., Fenton, B. W., von Gruenigen, V. E. (2013). Does enhanced "bundling" criteria improve outcomes? A comparative study of elective inductions. *Journal of Reproductive Medicine, 58*(9-10), 402-410. PMID: 24050029.

Citation 6 is a single institution interrupted time series study of an intervention that "bundled" a IHI set of eIOL quality criteria (>=39 weeks, normal fetal status; documentation of all Bishop score components including dilation, effacement, station, cervical position and consistency; and appropriate management of uterine tachysystole during IOL). Adoption of bundling criteria reduced the rate of Cesarean birth (12% vs. 21%), but did not change the rate of NICU admission. However, when the Bishop score was >6 then the rate of Cesarean birth was markedly reduced (4% vs. 19%), as was the rate of NICU admission (1% vs. 10%). The authors concluded that using the IHI eIOL bundle without requiring a specific Bishop score did not achieve optimal results. The current HERC guidance requires a Bishop score of >=6 for eIOL. This single study does not provide sufficient information to change that cutoff without the addition of other data.

7. Kolkman, D. G., Verhoeven, C. J., Brinkhorst, S. J., van der Post, J. A., Pajkrt, E., Opmeer, B. C., & Mol, B. J. (2013). The Bishop score as a predictor of labor induction success: A systematic review. *American Journal of Perinatology, 30*(8), 625-630. DOI: 10.1055/s-0032-1331024.

Citation 7 looked at the ability of Bishop Scores to predict Cesarean delivery among women undergoing IOL at term. The reported sensitivity/specificity of Bishop Scores of 4, 5 and 6, were 47%-75%, 61%-53%, and 78%-44%, respectively.

8. Mishanina, E., Rogozinska, E., Thatthi, T., Uddin-Khan, R., Khan, K. S., & Meads, C. (2014). Use of labour induction and risk of cesarean delivery: a systematic review and meta-analysis. *CMAJ: Canadian Medical Association Journal, 186*(9), 665-673. DOI: 10.1503/cmaj.130925.

Citation 8 is a SR/MA of RCTs examining the risk of Cesarean birth with IOL. The review found 157 eligible RCTs. The risk of Cesarean birth was overall lower with IOL than expectant management (RR 0.88, 95%CI 0.84-0.93), but the effect was statistically significant for term (37 to <42 weeks) and post-term (>42 weeks) gestations only. Meta-regression demonstrated that initial cervical score, indication for IOL and method of IOL did not change the main result. The risk of fetal death (0.50, 95% CI 0.25-0.99) and admission to a NICU (0.86, 95% CI 0.79-0.94)

were lower with IOL, but there was no impact on maternal mortality. This SR/MA included studies using different methods of IOL, with varying indications for IOL, and including women of different term gestational ages, pregnancy risk status, parity and degree of cervical readiness. This SR does not offer new information to the current HERC guidance.

9. NICE. (2014). *Induction of labour. NICE quality standard 60*. London: NICE. Retrieved from http://www.nice.org.uk/guidance/qs60/resources/guidance-induction-of-labour-pdf

   Background: NICE. (2014). *Clinical guideline: CG70: Induction of labour. Surveillance report.* London: NICE. Retrieved from http://www.nice.org.uk/guidance/cg70/documents/cg70-induction-of-labour-surveillance-review-decision-may-20142

   Background: NICE. (2013). *Induction of labour. Evidence update July 2013. A summary of selected new evidence relevant to NICE clinical guideline 70 'Induction of labor' (2008)*. London: NICE. Retrieved from http://www.nice.org.uk/guidance/cg70/evidence/cg70-induction-of-labour-evidence-update2

The resources listed above in Citation 9 relate to a core source used for the 2013 coverage guidance. NICE conducted surveillance of studies published through December 2013 to determine whether the 2008 IOL guideline should be updated. No new evidence that would impact the guideline was located. The next guideline review is scheduled for 2016.

The second resource represents the quality standards developed by NICE for use in quality of care monitoring and improvement for the NHS. The three quality standards statements relate to: 1) giving personalized information about the benefits and risks of IOL for a woman and her baby when IOL is offered; 2) not conducting outpatient IOL unless safety, support and audit procedures are in place; and 3) providing access to appropriate pain relief for women who are having IOL.

10. Nicholson, J. M., Kellar, L. C., Henning, G. F., Waheed, A., Colon-Gonzalez, M., & Ural, S. (2015). The association between the regular use of preventive labour induction and improved term birth outcomes: findings of a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology, 122*(6), 773-84. DOI: 10.1111/1471-0528.13301.

Citation 10 is a SR/MA re-analysis of four previously published studies of the AMOR-IPAT program of "preventive" IOL at ≥ 38 weeks for women with moderate risk factors such as gestational diabetes, chronic hypertension, etc. These studies were considered in the prior

review for the current HERC guidance and this article does not add new information to consideration of guidance update.

11. Rossi, A. C., & Prefumo, F. (2015). Pregnancy outcomes of induced labor in women with previous cesarean section: a systematic review and meta-analysis. *Archives of Gynecology & Obstetrics, 291*(2), 273-80. DOI: 10.1007/s00404-014-3444-9.

Citation 11 is a SR/MA of eight retrospective and one prospective cohort studies of IOL vs. spontaneous labor among women with a history of prior Cesarean birth. This review found that IOL increases the risk of uterine rupture and Cesarean birth, but given the largely retrospective nature of the studies and lack of expectant management control groups this data is of very poor quality and does not add new information to the prior HERC guidance.

12. Teixeira, C., Lunet, N., Rodrigues, T., & Barros, H. (2012). The Bishop Score as a determinant of labour induction success: a systematic review and meta-analysis. *Archives of Gynecology and Obstetrics, 286*(3), 739-753. DOI: 10.1007/s00404-012-2341-3.

Citation 12 was a SR/MA examining the odds of achieving a vaginal birth after IOL. Higher Bishop scores were associated with both vaginal birth and shorter induction to delivery time intervals. For each unit increase in Bishop Score the odds of vaginal birth was increased by 1.33 (95% CI 1.13-1.56), although there was fair heterogeneity among included studies.

13. Vijgen, S. M., Boers, K. E., Opmeer, B. C., Bijlenga, D., Bekedam, D. J., Bloemenkamp, K. W., … Scherjon, S. A. (2013). Economic analysis comparing induction of labour and expectant management for intrauterine growth restriction at term (DIGITAT trial). *European Journal of Obstetrics and Gynecology and Reproductive Biology, 170*(2), 358-363. DOI: 10.1016/j.ejogrb.2013.07.017.

Citation 13 is an alongside economic evaluation conducted with a Dutch RCT of IOL vs. expectant management for suspected IUGR beyond 36 completed weeks of gestation. Both strategies generated comparable costs (7106 euros for IOL vs. 6995 euros for expectant monitoring), although the distribution of antepartum and intrapartum costs differed. Costs were also lower in the expectant management group prior to 38 weeks and in the IOL group after that point. The authors concluded that, given the clinical and economic results of the RCT, that expectant management prior to 38 weeks is a reasonable strategy.

14. Vijgen, S. M., Koopmans, C. M., Opmeer, B. C., Groen, H., Bijlenga, D., Aarnoudse, J. G., … van Pampus, M. G. (2010). An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT

trial). *BJOG. An International Journal of Obstetrics and Gynaecology, 117*(13), 1577-1585. DOI: 10.1111/j.1471-0528.2010.02710.x.

Citation 14 is an economic study done in conjunction with a Dutch RCT of IOL vs. expectant management of women with gestational hypertension or pre-eclampsia between 36w + 0d and 41w + 0d of gestation. More costs were generated with expectant monitoring compared to IOL (7908 euros vs 7077 euros). This 11% difference was primarily due to costs originating in the antepartum period. During delivery, more costs were generated by women in the IOL group. There were essentially no differences for costs in the postpartum period. Given the differences in the systems of care between the Netherlands and the U.S., any direct comparability of costs is not possible.

15. Wood, S., Cooper, S., & Ross, S. (2014). Does induction of labour increase the risk of caesarean section? A systematic review and meta-analysis of trials in women with intact membranes. *BJOG. An International Journal of Obstetrics and Gynaecology, 121*(6), 674-685. DOI: 10.1111/1471-0528.12328.

Citation 15 is a SR/MA of RCTs studying IOL vs. expectant management among women with intact amniotic membranes. Of 37 included studies, 27 included women with uncomplicated pregnancies at 37 to 42 weeks of gestation and the remaining 10 included women with medical and obstetric complications (suspected macrosomia, twins, oligohydramnios, IUGR, hypertension and high risk score for Cesarean birth). The authors concluded that a policy of eIOL reduces the risk of Cesarean birth among women beyond their due dates (OR 0.85, 95% CI 0.76-0.95) and among women with obstetric and medical complications (OR 0.81, 95% CI 0.69-0.95). The odds were similar among both groups when only high quality trials were included, but the CI for the group with complications was no longer statistically significant. The authors noted that only one RCT in the complicated pregnancy group was actually designed to assess the outcome of Cesarean birth and that the effects observed across the included RCTs could, therefore, be due to non-treatment effects and that conclusions based on these data may be premature.

16. World Health Organization (WHO). (2011). *Induction of labour.* Geneva, Switzerland: WHO. Retrieved from http://apps.who.int/iris/bitstream/10665/44531/1/9789241501156_eng.pdf

Citation 16 is largely in alignment with current HERC guidance. The only strong recommendation in the WHO guideline is for IOL among women with prelabor rupture of membrane. There is a weak recommendation for IOL for women at or beyond 41 weeks (41 w. + 0 d.) of gestation. There are weak recommendations against IOL for: 1). women with

uncomplicated pregnancy who are less than 41 weeks, 2). including those for whom gestational diabetes is the only abnormality; and 3). women with suspected fetal macrosomia. The WHO panel found insufficient evidence to guide management of women with uncomplicated twin gestation at or near term and so no recommendation was made.

Summary

This rescan for the HERC's IOL guidance found evidence that largely comported with and supported existing coverage guidance. Little contradictory or newer evidence was identified that would be likely to change the current coverage recommendations or the strength of those recommendations. The exception is the WHO recommendation against induction without a specific indication for women at fewer than 41 weeks of gestation. The current coverage guidance is silent on the subject of gestational age and IOL for twin pregnancy or pregnancy complicated by gestational hypertension or suspected IUGR. The rescan may have identified studies that could help to identify a target gestational age for expectant monitoring vs. IOL. However, the HERC guidance currently has weak recommendations for these conditions and so largely leaves the decision up to clinical judgment. The rescan identified data confirming that outcomes for eIOL are improved with higher Bishop Score and no need for cervical ripening prior to IOL. The guidance currently recommends a minimum Bishop score of ≥ 6, although some newer evidence indicates that setting a cutoff higher (>6) may improve both maternal and neonatal outcomes. These would not likely be substantial changes to the guidance at present, but the HERC could consider a targeted search relative to each potential indication and modifying factor (such as Bishop Score) at the next rescan. Three economic studies found positive economic results for IOL in the case of gestations over 41 weeks, maternal hypertensive disease and suspected IUGR.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "induction of labor [or labour]," "elective induction," and "labor induce." Searches of core sources were limited to citations published after 2009 (the last search dates of the original evidence sources).

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2009 (the last search dates of the initial evidence sources).

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Management of Recurrent Acute Otitis Media in Children – 2015 Rescanning Summary

Subcommittee: Evidence-based Guidelines Subcommittee (HERC approved August 2013)

EbGS Recommendation: Develop a new coverage guidance to update this topic.

Bottom Line: The evidence for adenoidectomy and/or tympanostomy tubes for recurrent acute otitis media (AOM) is mixed with several new publications since the initial coverage guidance was issued. There appears to be no new summary evidence on the effectiveness of prophylactic antibiotics for recurrent AOM, though it should be noted that AAP guidelines recommend against it.

Coverage Recommendation (Box Language)

Prophylactic antibiotics should be covered for recurrent acute otitis media.*

Tympanostomy tubes may be covered for acute otitis media only for recurrent acute otitis media.

Adenoidectomy or adenotonsillectomy should not be covered for the treatment of recurrent acute otitis media.

**Recurrent acute otitis media is defined here as three or more episodes in six months or four or more episodes in one year.*

Note: Coverage guidance for chronic otitis media with effusion is addressed in a separate document.

Scope Statement

Population description	Children with recurrent acute otitis media (AOM) *Population scoping notes: None*
Intervention(s)	Prophylactic or suppressive antibiotics, tympanostomy tubes (grommets), tonsillectomy and/or adenoidectomy (note that these interventions may be used alone, serially or in combination) *Intervention exclusions: None*
Comparator(s)	Usual care, episodic treatment of AOM

Outcome(s) (up to five)	*Critical*: Severe infection (e.g., systemic infection, sepsis, meningitis, locally invasive infection), clinically significant hearing loss, speech delay *Important*: Treatment harms, acute otitis media episodes *Outcomes considered but not selected for GRADE table:* Missed school days, school performance/academic achievement
Key questions	1. What is the comparative effectiveness of interventions (alone, serially, or in combination) for recurrent acute otitis media? a. Are there subpopulations of children with recurrent acute otitis media who are more likely to benefit from prophylactic interventions? 2. What are the harms of interventions for recurrent acute otitis media?

Original Evidence Sources

Leach, A. J., & Morris, P.S. (2006). Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database of Systematic Reviews*, *4*(CD004401), 1-70. [Assessed as up-to-date: 5 AUG 2010]. Retrieved from http://summaries.cochrane.org/CD004401/antibiotics-to-prevent-acute-earinfections-in-children

McDonald, S., Langton Hewer, C. D., & Nunez, D. A. (2008). Grommets (ventilation tubes) for recurrent acute otitis media in children. *Cochrane Database of Systematic Reviews*, *4*(CD 004741), 1-14. [Assessed as up-to-date: 10 JAN 2011]. Retrieved from http://summaries.cochrane.org/CD004741/grommets-ventilation-tubes-for-recurrentacute-otitis-media-in-children

Shekelle, P. G., Takata, G., Newberry, S.J., Coker, T., Limbos, M., Chan, L. S., … Shanman, R. (2010). *Management of Acute Otitis Media: Update.* Evidence Report/Technology Assessment No. 198. (Prepared by the RAND Evidence-Based Practice Center under Contract No. 290 2007 10056 I). Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK56132/

Scanning Results

1. Boonacker, C. W., Rovers, M. M., Browning, G. G., Hoes, A. W., Schilder, A. G., & Burton, M. J. (2014). Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. *Health Technology Assessment, 18*(5), 1-117.

Citation 1 is a health technology assessment by the NHS and includes a meta-analysis of 10 trials of adenoidectomy with or without grommets. In the meta-analysis, adenoidectomy with or without grommets had a failure rate (defined as >4 episodes of AOM over 12 months) of 32% compared with 45% in the group that did not undergo adenoidectomy. The benefit of adenoidectomy for recurrent AOM appeared to be greatest in children under the age of 2 years.

2. Canadian Agency for Drugs and Technologies in Health (CADTH). (2014). *Tympanostomy tube insertion system for children with otitis media*. Ottawa: CADTH. Retrieved from https://www.cadth.ca/sites/default/files/pdf/EH0018_TympanostomyTubeInsertionDelivery_e.pdf

Citation 2 is a CADTH brief summary on the TULA system for placing tympanostomy tubes in the outpatient setting using local anesthesia only. Based on three single-arm, open-label, prospective trials the TULA system appears to be safe and cost-effective. It should be noted that there are competing technologies under development.

3. Cheong, K. H., & Hussain, S. S. (2012). Management of recurrent acute otitis media in children: systematic review of the effect of different interventions on otitis media recurrence, recurrence frequency and total recurrence time. *Journal of Laryngology & Otology, 126*(9), 874-85.

Citation 3 is a systematic review that includes seven studies examining various interventions for recurrent AOM. The authors conclude that prophylactic antibiotics and adenoidectomy both reduce recurrence of AOM, but tympanostomy tubes do not.

4. Courter, J. D., Baker, W. L., Nowak, K. S., Smogowicz, L. A., Desjardins, L. L., Coleman, C. I., & Girotto, J. E. (2010). Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis. *Annals of Pharmacotherapy, 44*(3), 471-478.

Citation 4 is a meta-analysis of studies comparing macrolides to beta-lactam antibiotics for AOM. It is out of scope.

5. Gaboury, I., Coyle, K., Coyle, D., & Le Saux, N. (2010). Treatment cost effectiveness in acute otitis media: a watch-and-wait approach versus amoxicillin. *Paediatrics and Child Health, 15*(7), e14-e18.

Citation 5 is a Canadian cost-effectiveness study comparing watchful-waiting to amoxicillin treatment for AOM. It is out of scope.

6. Gisselsson-Solen, M. (2014). The importance of being specific – a meta-analysis evaluating the effect of antibiotics in acute otitis media. *International Journal of Pediatric Otorhinolaryngology, 78*(8), 1221-1227.

Citation 6 is meta-analysis that addresses methodologic issues in the selection of outcomes for trials of antibiotic treatment of AOM. It is out of scope.

7. Hellstrom, S., Groth, A., Jorgensen, F., Pettersson, A., Ryding, M., Uhlen, I., & Bostrom, K. B. (2011). Ventilation tube treatment: a systematic review of the literature. *Otolaryngology – Health & Neck Surgery, 145*(3), 383-95.

Citation 7 is a systematic review of 63 studies of "secretory otitis media." The authors conclude that tympanostomy tubes are associated with improve QoL but there is insufficient evidence of an effect on recurrent AOM.

8. Kozyrskyj, A. L., Klassen, T. P., Moffatt, M., & Harvey, K. (2010). Short-course antibiotics for acute otitis media. *Cochrane Database of Systematic Reviews*, Issue 9. DOI: 10.1002/14651858.CD001095.pub2.

Citation 8 is a Cochrane review of short-course antibiotic treatment of AOM. It is out of scope.

9. Lieberthal, A. S., Carroll, A. E., Chonmaitree, T., Ganiats, T. G., Hoberman, A., Jackson, M. A., … Tunkel, D. E. (2013). The diagnosis and management of acute otitis media. *Pediatrics, 131*(3), e964-99.

Citation 9 is a CPG from the American Academy of Pediatrics. The guidelines state that prophylactic antibiotics should not be prescribed for the treatment of recurrent AOM (evidence level: B, strength: recommendation). Tympanostomy tubes can be offered for recurrent AOM (evidence level: B, strength: option).

10. Lous, J., Ryborg, C. T., & Thomsen, J. L. (2011). A systematic review of the effect of tympanostomy tubes in children with recurrent acute otitis media. *International Journal of Pediatric Otohinolaryngology, 75*(9), 1058-61.

Citation 10 is a systematic review of tympanostomy tubes for recurrent AOM. The authors conclude that 2 to 5 children need to receive tympanostomy tubes in order to prevent one episode of recurrent AOM over 6 months. The authors note that this appears to be similar to the effects of six months of prophylactic antibiotic treatment.

11. Mikals, S. J., & Brigger, M. T. (2014). Adenoidectomy as an adjuvant to primary tympanostomy tube placement: a systematic review and meta-analysis. *JAMA Otolaryngology - Head and Neck Surgery, 140*(2), 95-101.

Citation 11 is a SR and MA of 15 trials of adenoidectomy in addition to tympanostomy tube placement for treatment of recurrent AOM, otitis media with effusion, or otorrhea. The study results were mixed and heterogeneous, but in the meta-analysis addition of adenoidectomy reduced the need for repeated tympanostomy tubes, although the effects appeared to be attenuated in children under the age of 4 years.

12. Rosenfeld, R. M., Schwartz, S. R., Pynnonen, M. A., Tunkel, D. E., Hussey, H. M., Fichera, J. S., … Schellhase, K. G. (2013). Clinical practice guideline: tympanostomy tubes in children. *Otolaryngology - Head and Neck Surgery, 149*(1 Suppl):S1-35.

Citation 12 is a CPG from the American Academy of Otolaryngology – Head and Neck Surgery. The guidelines recommend that tympanostomy tubes should not be offered for treatment of recurrent AOM unless a middle ear effusion is present at the time of evaluation for tubes.

13. Subcommittee of Clinical Practice Guideline for Diagnosis and Management of Acute Otitis Media in Children (Japan Otological Society, Japan Society for Pediatric Otorhinolaryngology, Japan Society for Infectious Diseases in Otolaryngology). (2012). Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan. *Auris, Nasus, Larynx, 39*(1), 1-8.

Citation 13 is multi-society CPG from several ENT societies in Japan pertaining to treatment of AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

14. Thanaviratananich, S., Laopaiboon, M., & Vatanasapt, P. (2013). Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. *Cochrane Database of Systematic Reviews*, Issue 12. DOI: 10.1002/14651858.CD004975.pub3.

Citation 14 is a Cochrane review comparing the effectiveness of various dosing regimens for the treatment of AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

15. Thorton, K., Parrish, F., & Swords, C. (2011). Topical vs. systematic treatments for acute otitis media. *Pediatric Nursing, 37*(5), 263-7.

Citation 15 is a narrative review of treatment strategies for AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

16. Toll, E. C., & Nunez, D. A. (2012). Diagnosis and treatment of acute otitis media: review. *Journal of Laryngology & Otology, 126*(10), 976-83.

Citation 16 is a narrative review of the diagnosis and treatment of AOM. It does not specifically address the treatment of recurrent AOM except to briefly note that tympanostomy tubes reduce recurrent AOM.

17. van den Aardweg, M. T. A., Schilder, A. G. M., Herkert, E., Boonacker, C. W. B., & Rovers, M. M. (2010). Adenoidectomy for otitis media in children. *Cochrane Database of Systematic Reviews*, Issue 1. Art. DOI: 10.1002/14651858.CD007810.pub2.

Citation 17 is a Cochrane review of adenoidectomy compared with tympanostomy tubes or non-surgical management in children with otitis media with effusion. The authors conclude that the studies of adenoidectomy did not demonstrate a significant benefit in reducing episodes of AOM.

18. Venekamp, R. P., Sanders, S. L., Glasziou, P. P., Del Mar, C. B., & Rovers, M. M. (2015). Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews*, Issue 6. DOI: 10.1002/14651858.CD000219.pub4.

Citation 18 is a Cochrane review of antibiotic treatment for AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

19. Venekamp, R. P., Damoiseaux, R. A. M. J. & Schilder, A. G. M. (2014). Acute otitis media in children. *BMJ Clinical Evidence, 09*, 301-322.

Citation 19 is a BMJ Clinical Evidence brief on the diagnosis and management of AOM. It does not specifically address the treatment of recurrent AOM and is thus out of scope.

20. Washington Health Technology Assessment (WA HTA). (2015). *Tympanostomy tubes in children – draft evidence report*. Olympia, WA: WA HTA. Retrieved Anugust 12, 2015 from http://www.hca.wa.gov/hta/Documents/tympan_tubes_draft_report_073115.pdf

Citation 20 is a draft WA HTA report on the use of tympanostomy tubes in children. The report only briefly addresses the population of children with recurrent AOM but notes that there is little evidence of efficacy or only small short-term benefits for tubes in the management of recurrent AOM. It also notes that current guidelines recommend against prescribing prophylactic antibiotics for recurrent AOM.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "otitis media," "tonsillectomy," "adenoidectomy," and "tympanostomy tube." Searches of core sources were limited to citations published after 2009.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2009.

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

MRI for Breast Cancer Diagnosis – 2015 Rescanning Summary

Subcommittee: Health Technology Assessment Subcommittee (HERC approved May 2013)

HTAS Recommendation: Reaffirm the existing coverage guidance and reconsider the need to update it during the regular two-year review cycle.

Bottom Line: Additional evidence suggests that MRI in patients with recently diagnosed breast cancer does not improve clinical outcomes, but may result in false-positive test results and overtreatment with more aggressive surgical procedures.

Coverage Recommendation (Box Language)

In women with recently diagnosed breast cancer, preoperative or contralateral MRI of the breast should not be a covered service.

Scope Statement:

Population description	Adults with recently diagnosed breast cancer *Population scoping notes: None*
Intervention(s)	Breast MRI *Intervention exclusions: None*
Comparator(s)	Usual care, including other imaging modalities
Outcome(s) (up to five)	**Critical:** All-cause mortality, cancer-specific mortality **Important:** Progression-free survival, false-positive test results, quality of life *Considered but not selected for GRADE table: Change in surgical or non-surgical treatment plan*
Key questions	1. What is the comparative effectiveness of breast MRI after the diagnosis of breast cancer for improving patient outcomes? 2. What are the harms of breast MRI after the diagnosis of breast cancer? Contextual Question 1. How often do the results of MRI after breast cancer diagnosis lead to changes in the surgical or non-surgical treatment plan?

Original Evidence Source

Washington State Health Care Authority Health Technology Assessment Program. (2010). *HTA Report: Breast MRI in diagnosis and treatment of cancer in women at high risk*. Olympia, WA: Health Technology Assessment Program. Retrieved from http://www.hta.hca.wa.gov/documents/breast_mri_072310_final.pdf

Scanning Results

1. Alberta Provincial Breast Tumour Team. (2012). *Magnetic resonance imaging for breast cancer screening, pre-operative assessment, and follow-up*. Edmonton (Alberta): Alberta Health Services, Cancer Care. Retrieved from http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-br007-mri.pdf

Citation 1 is an Alberta Health Services clinical practice guideline addressing the use of MRI for screening, pre-operative assessment, or follow-up of breast cancer. It offers the following pertinent guidance:

"Pre-operative MRI may be considered in the following circumstances:
• Biopsy proven axillary nodal adenocarcinoma with no primary identified on mammography, ultrasound, and physical examination.
• Discordant clinical and mammogram/ultrasound findings.

Pre-operative MRI may be used in the following situations where the patient desires breast conserving surgery and:
• There is high risk for multifocal/multicentric disease.
• The extent of disease is unclear.

MRI may be used for breast cancer evaluation before, during and after neoadjuvant therapy to help evaluate response to systemic treatments.
• MRI may overestimate response to neoadjuvant chemotherapy and should not be used to plan post-chemotherapy breast conserving surgery.
• MRI accurately predicts lack of response to neoadjuvant chemotherapy and may be used to support a change in therapy. "

2. Brasic, N., Wisner, D. J., & Joe, B. N. (2013). Breast MR imaging for extent of disease assessment in patients with newly diagnosed breast cancer. *Magnetic Resonance Imaging Clinics of North America, 21*(3), 519-32.

Citation 2 is a non-systematic narrative review of MRI for breast cancer. It would not meet criteria for inclusion in an updated coverage guidance.

3. Bruening, W., Uhl, S., Fontanarosa, J., Reston, J., Treadwell, J., & Schoelles, K. (2012). *Noninvasive diagnostic tests for breast abnormalities: Update of a 2006 review.* Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from www.effectivehealthcare.ahrq.gov/reports/final.cfm

Citation 3 is an AHRQ review of various non-invasive imaging modalities for evaluation of abnormalities identified on routine screening. The review does not explicitly address MRI for patients with recently diagnosed breast cancer and is therefore out of scope.

4. Chen, X., Li, W. L., Zhang, Y. L., Wu, Q., Guo, Y. M., & Bai, Z. L. (2010). Meta-analysis of quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesions. *BMC Cancer, 10*, 693.

Citation 4 is a SR of a quantitative diffusion weighted MR technique for the diagnosis of breast cancer. It is therefore out of scope.

5. Cooper, K. L., Meng, Y., Harnan, S., Ward, S. E., Fitzgerald, P., Papaioannou, D., … Lorenz, E. (2011). Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: systematic review and economic analysis. *Health Technology Assessment, 15*(4), 1-134.

Citation 5 is a SR and economic evaluation of PET, MRI, and various lymph node sampling techniques for the diagnosis of axillary lymph node metastases. The summary sensitivity and specificity of MRI ranged from 64%-98% and 73%-100% respectively depending on the MR technique used. In the cost-effectiveness analysis, MRI was the dominant strategy, though this British economic analysis may be too indirect to influence new coverage guidance.

6. Harnan, S. E., Cooper, K. L., Meng, Y., Ward, S. E., Fitzgerald, P., Papaioannou, D., … Wyld, L. (2011). Magnetic resonance for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis. *European Journal of Surgical Oncology, 37*(11), 928-36.

Citation 6 is a SR of studies examining MRI for the assessment of axillary lymph node status in early stage breast cancer. The sensitivity and specificity of ultrasmall super-paramagnetic iron oxide MRI were 98% and 96% respectively. However, the authors conclude that “current

estimates of sensitivity and specificity do not support replacement of SLNB [sentinel lymph node biopsy] with any current MRI technology in this patient group.

7. Houssami, N., Turner, R., Macaskill, P., Turnbull, L. W., McCready, D. R., Tuttle, T. M., … Solin, L. J. (2014). An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. *Journal of Clinical Oncology, 32*(5), 392-401.

Citation 7 is a patient-level MA of the effects of preoperative MRI on local and distant recurrence in patients with breast cancer. At eight years, there was no difference in local or distant recurrence in the MRI and no-MRI groups.

8. Houssami, N., Turner, R., & Morrow, M. (2013). Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. *Annals of Surgery, 257*(2), 249-55.

Citation 8 is a SR of studies on the effects of preoperative MRI on surgical outcomes. The authors conclude that "evidence showed that MRI significantly increased mastectomy rates and suggests an unfavorable harm-benefit ratio for routine use of preoperative MRI in BC [breast cancer]. We found weak evidence that MRI reduced re-excision surgery in patients with ILC [invasive lobular cancer] — although this was at the expense of increased mastectomies—and overall patient benefit from MRI in ILC is not clear from this study."

9. Institute for Clinical Systems Improvement (ICSI). (2012). Diagnosis of breast disease. Bloomington, MN: ICSI. Retrieved from https://www.icsi.org/_asset/v9l91q/DxBrDis.pdf

Citation 9 is an ICSI report on the initial diagnosis of breast cancer. It is therefore out of scope.

10. Medeiros, L. R., Duarte, C. S., Rosa, D. D., Edelweiss, M. I., Edelweiss, M., Silva, F. R., … Rosa, M. I. (2011). Accuracy of magnetic resonance in suspicious breast lesions: a systematic quantitative review and meta-analysis. *Breast Cancer Research & Treatment, 126*(2), 273-85.

Citation 10 is a SR examining the use of MRI for the initial diagnosis of suspicious breast lesions identified on screening. It is therefore out of scope.

11. Meng, Y., Ward, S., Cooper, K., Harnan, S., & Wyld, L. (2011). Cost-effectiveness of MRI and PET imaging for the evaluation of axillary lymph node metastases in early stage breast cancer. *European Journal of Surgical Oncology, 37*(1), 40-6. Retrieved from http://ac.els-cdn.com/S0748798310005238/1-s2.0-S0748798310005238-main.pdf?_tid=709ff45c-

4211-11e5-a1ee-00000aacb360&acdnat=1439508017_3059855702ecf908c89280499139c38e

Citation 11 is a cost-effectiveness study of MRI of imaging vs sentinel lymph node biopsy for evaluation of axillary lymph node metastases in early breast cancer. The summary sensitivity and specificity of MRI were both 90%. From the perspective of the British NHS, MRI was the most cost-effective strategy for diagnosing axillary lymph node metastases, but this British economic analysis may be too indirect to influence new coverage guidance.

12. Parsyan, A., Algahtani, A., Mesurolle, B., & Meterissian, S. (2013). Impact of preoperative breast MRI on surgical decision making and clinical outcomes: a systematic review. *World Journal of Surgery, 37*(9), 2134-9.

Citation 12 is a SR of studies examining the effects of preoperative MRI on surgical decision-making and clinical outcomes. The authors conclude that "Preoperative MRI is a highly sensitive but nonspecific method that leads to changes in surgical management with increased numbers of more extended surgical interventions. It appears that a relatively large proportion of MRI-driven changes in surgical management result in overtreatment without conclusively proven beneficial effects on such clinical outcomes as decrease in reoperation rates or improved patient survival."

13. Plana, M. N., Carreira, C., Muriel, A., Chiva, M., Abraira, V., Emparanza, J. I., … Zamora, J. (2012). Magnetic resonance imaging in the preoperative assessment of patients with primary breast cancer: systematic review of diagnostic accuracy and meta-analysis. *European Radiology, 22*(1), 26-38.

Citation 13 is a systematic review of studies of MRI in the preoperative assessment of breast cancer. The authors conclude that "MRI shows high diagnostic accuracy, but MRI findings should be pathologically verified because of the high FP [false positive] rate. Future research on this emerging technology should focus on patient outcome as the primary end-point."

14. Prevos, R., Smidt, M. L., Tjan-Heijnen, V. C., van Goethem, M., Beets-Tan, R. G., Wildberger, J. E., & Lobbes, M. B. (2012). Pre-treatment differences and early response monitoring of neoadjuvant chemotherapy in breast cancer patients using magnetic resonance imaging: a systematic review. *European Radiology, 22*(12), 2607-16.

Citation 14 is a SR of studies examining the role of MRI for assessing response to neoadjuvant chemotherapy. The authors conclude that "[e]vidence on distinguishing responders and non-responders to neoadjuvant chemotherapy using pretreatment MRI, as well as using MRI for

early response monitoring, is weak and based on underpowered study results and heterogeneous study design. Thus, the value of breast MRI for response evaluation has not yet been established."

15. Shao, Z., Wang, H., Li, X., Liu, P., Zhang, S., & Cao, S. (2013). Morphological distribution and internal enhancement architecture of contrast-enhanced magnetic resonance imaging in the diagnosis of non-mass-like breast lesions: a meta-analysis. *Breast Journal, 19*(3), 259-268.

Citation 15 is a MA of studies examining MRI for the initial diagnosis of breast cancer in non-mass like breast lesions. It is therefore out of scope.

16. Wu, L. M., Hu, J. N., Gu, H. Y., Hua, J., Chen, J., & Xu, J. R. (2012). Can diffusion-weighted MR imaging and contrast-enhanced MR imaging precisely evaluate and predict pathological response to neoadjuvant chemotherapy in patients with breast cancer? *Breast Cancer Research & Treatment, 135*(1), 17-28.

Citation 16 is a SR and MA of studies examining the use of diffusion-weighted MRI and contrast-enhanced MRI for monitoring response to neoadjuvant chemotherapy. The authors conclude that DW-MRI is highly sensitive and CE-MRI is highly specific in predicting pathological response to neoadjuvant chemotherapy. The authors propose that future studies should examine the combination of these tests for assessing response to neoadjuvant treatment.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "MRI breast," "MRI breast diagnos*," and "magnetic resonance imaging breast diagnos*." Searches of core sources were limited to citations published after 2009.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2009.

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Neuroimaging for Headache – 2015 Rescanning Summary

Subcommittee: Evidence-based Guidelines Subcommittee (HERC approved August 2013)

EbGS Recommendation: Reaffirm the existing coverage guidance and reconsider the need to update it during the regular two-year review cycle.

Bottom Line: There continues to be very limited good-quality evidence on the utility of neuroimaging for headache. In general, the sources reviewed below recommend that neuroimaging should not be obtained in the evaluation of primary headache disorders without red-flags. There is some minor variability in the definition of red-flag features, and in most cases these determinations are made on the basis of expert opinion. Most of the red-flag features proposed in other guidelines are captured in the current HERC coverage guidance.

Coverage Recommendation (Box Language)

Neuroimaging is not recommended for coverage in patients with a defined tension or migraine type of headache, or a variation of their usual headache (e.g. more severe, longer in duration, or not responding to drugs).

Neuroimaging is recommended for coverage with headache when a red flag* is present.

*The following represent red flag conditions for underlying abnormality with headache:

- new onset or change in headache in patients who are aged over 50
- thunderclap headache: rapid time to peak headache intensity (seconds to 5 min)
- focal neurologic symptoms (e.g. limb weakness, lack of coordination, numbness or tingling)
- non-focal neurological symptoms (e.g. altered mental status, dizziness)
- abnormal neurological examination
- headache that changes with posture
- headache waking the patient up (Note: migraine is the most frequent cause of morning headache)
- headache precipitated by physical exertion or Valsalva maneuver (e.g. coughing, laughing, straining)
- patients with risk factors for cerebral venous sinus thrombosis
- jaw claudication
- nuchal rigidity
- new onset headache in a patient with a history of human immunodeficiency virus (HIV) infection

- new onset headache in a patient with a history of cancer
- cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), or short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA)

Scope Statement

Population description	Adults and children with non-traumatic, acute or chronic headache
Intervention(s)	MRI or CT head/brain, with or without contrast enhancement *Intervention exclusions: None*
Comparator(s)	Usual care, no neuroimaging
Outcome(s) (up to five)	**Critical:** Morbidity from significant intracranial abnormalities **Important:** Headache-free days, quality of life, harms from radiation exposure, harms from incidental findings *Outcomes considered but not selected for GRADE table: None*
Key questions	1. What is the comparative effectiveness of neuroimaging for headache in improving patient outcomes or detecting significant intracranial abnormalities? a. Does the effectiveness of neuroimaging for headache vary based on acuity? 2. What are the evidence-supported red-flag features which are indications for neuroimaging for headache? a. Do the evidence-supported red-flag features which indicate neuroimaging vary based on acuity? 3. What are the harms of neuroimaging for headache?

Original Evidence Sources

Clark, E. E., Little, A., & King, V. (2010). *Red flags and imaging in headache*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

Key Sources Cited in MED Report:

Detsky, M. E., McDonald, D. R., Baerlocher, M. O., Tomlinson, G. A., McCrory, D. C., & Booth, C. M. (2006). Does this patient with headache have a migraine or need neuroimaging? *JAMA*, *296*(10), 1274-1283. DOI:10.1001/jama.296.10.1274.

Frishberg, B. M., Rosenberg, J. H., Matchar, D. B., McCrory, D. C., Pietrzak, M. P., Rozen, T. D., & Silberstein, S. D. (2000). Evidence-based guidelines in the primary care setting: Neuroimaging in patients with nonacute headache. US Headache Consortium. Minneapolis, MN: American Academy of Neurology. Retrieved from http://www.aan.com/professionals/practice/pdfs/gl0088.pdf

McCormack, R. F. & Hutson, A. (2010). Can computed tomography angiography of the brain replace lumbar puncture in the evaluation of acute-onset headache after a negative noncontrast cranial computed tomography scan? *Academic Emergency Medicine, 17*(4), 444-451. DOI: 10.1111/j.1553-2712.2010.00694.x.

Scottish Intercollegiate Guidelines Network. (2008). *Diagnosis and Management of Headaches in Adults.* A National Clinical Guideline. Edinburg: Scottish Intercollegiate Guidelines Network. Retrieved from http://www.sign.ac.uk/pdf/qrg107.pdf

Scanning Results

1. Alexiou, G. A. & Argyropoulou, M. I. (2013) Neuroimaging in childhood headache: A systematic review. *Pediatric Radiology, 43*(7):777-784. DOI: 10.1007/s00247-013-2692-3.

Citation 1 is a systematic review of seventeen studies examining the utility of neuroimaging for children with headaches. Of 3,260 children who had undergone neuroimaging for headache, only 82 (2.5%) had imaging findings that led to a change in management, and among these patients only 4 had normal neurologic exams. The overall conclusion is that neuroimaging for headache in children is generally low yield and should be limited to those with "a suspicious clinical history, abnormal neurologic findings or other physical signs suggestive of intracranial pathology."

2. Beithon, J., Gallenberg, M., Johnson, K., Kildahl, P., Krenik, J., Liebow, M., … Swanson, J. (2013). Diagnosis and treatment of headache. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Jan. Retrieved from http://bit.ly/Headache0113

Citation 2 is a guideline from the Institute for Clinical Systems Improvement (ICSI). It is focused mainly on the diagnosis and management of primary headache disorders, for which neuroimaging is not needed for the diagnosis. The guideline offers the following causes for concern:

- Subacute and/or progressive headaches that worsen over time (months)
- A new or different headache or a statement by a headache patient that "this is the worst headache ever"
- Any headache of maximum severity at onset
- Headaches of new onset after the age of 50 years old
- Persistent headache precipitated by a Valsalva maneuver such as cough, sneeze, bending or with exertion (physical or sexual)
- Evidence such as fever, hypertension, myalgias, weight loss or scalp tenderness suggesting a systemic disorder
- Neurological signs that may suggest a secondary cause. For example: meningismus, confusion, altered levels of consciousness, changes or impairment of memory, papilledema, visual field defect, cranial nerve asymmetry, extremity drifts or weaknesses, clear sensory deficits, reflex asymmetry, extensor plantar response, or gait disturbances
- Seizures

According to the ICSI algorithm, any of the above signs should prompt consideration of secondary headache disorders and additional diagnostic testing (including neuroimaging) or referral for specialty consultation is warranted.

3. Douglas, A. C., Wippold, F. J. II, Broderick, D. F., Aiken, A. H., Amin-Hanjani, S., Brown, D. C., … Zipfel G. J. (2013). ACR Appropriateness Criteria® headache. [online publication]. Reston (VA): American College of Radiology (ACR).

Citation 3 is the American College of Radiology Appropriateness Criteria for headaches in adults. In general, imaging is usually not appropriate for chronic headaches without new features or abnormalities on neurologic exam. Some form of neuroimaging (e.g., MRI, CT, angiography) may be appropriate or is usually appropriate in the following scenarios:

- Chronic headache with new feature or neurologic deficit
- Sudden onset of severe headache

- Sudden onset of unilateral headache or suspected carotid or vertebral dissection
- Headache of trigeminal autonomic origin
- Headache of skull base, orbital, or periorbital origin
- Headache with suspected intracranial complication of sinusitis and/or mastoiditis
- Headache of oromaxillofacial origin
- New headache in elderly patients, ESR>55, temporal tenderness
- New headache in a cancer patient or immunocompromised individual
- New headache with suspected meningitis/encephalitis
- New headache in a pregnant woman
- New headache with focal neurologic deficit or papilledema
- Positional headache
- Headache associated with cough, exertion, or sexual activity
- Post-traumatic headache

4. Hayes, L. L., Coley, B. D., Karmazyn, B., Dempsey-Robertson, M. E., Dillman, J. R., Dory, C. E., … Wootton-Gorges, S. L. (2012). ACR Appropriateness Criteria® headache - child. [online publication]. Reston (VA): American College of Radiology (ACR).

Citation 4 is the American College of Radiology Appropriateness Criteria for headaches in children. In general, imaging is usually not appropriate for primary headache disorders (chronic or recurrent headache including migraine without permanent neurologic signs or signs of increased intracranial pressure). Some form of neuroimaging (e.g., MRI, CT, angiography) may be appropriate or is usually appropriate in the following scenarios:

- Headache with signs of increased intracranial pressure or positive neurologic signs
- High-intensity headache of abrupt onset

5. Medical Advisory Secretariat. (2010). Neuroimaging for the evaluation of chronic headaches: an evidence-based analysis. Ontario Health Technology Assessment Service. 2010]; 10(26) 1-57. Retrieved from: http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_Headache_20101222.pdf

Citation 5 is a health technology assessment and economic analysis from the Medical Advisory Secretariat of the Ontario Ministry of Health and Long-Term Care. Its focus is on the use of neuroimaging in people with chronic headache with a normal neurologic exam. Of note, the GRADE quality of evidence reported for this review was low to very low. The overall pretest probability of intracranial abnormalities in people with chronic headaches without neurologic

findings is 0.9%. Summary likelihood ratios for detecting significant intracranial abnormalities were statistically significant for the following findings/ characteristics:

- Abnormal neurologic exam (+LR 5.3, -LR 0.71)
- Undefined headache (+LR 3.8, -LR 0.66)
- Headache aggravated by exertion or Valsalva (+LR 2.3, -LR 0.70)
- Headache with vomiting (+LR 1.8, -LR 0.47)
- Cluster-type headache (+LR 11, -LR 0.95 [NS])
- Headache with aura (+LR 3.2, -LR 0.51 [NS])

The review did not find evidence that neuroimaging reduced anxiety at 1 year.

6. National Clinical Guideline Centre. (2012). Headaches: diagnosis and management of headaches in young people and adults. London (UK): National Institute for Health and Clinical Excellence (NICE).

Citation 6 is a NICE guideline on headache in young people and adults. NICE recommends that people with tension-type or migraine headache should not be referred for imaging if they do not have signs or symptoms of secondary headache. Signs and symptoms of secondary headache are

- Worsening headache with fever
- Sudden-onset headache reaching maximum intensity within 5 minutes
- New-onset neurologic deficit
- New-onset cognitive dysfunction
- Change in personality
- Impaired level of consciousness
- Recent head trauma (typically within the past 3 months)
- Headache triggered by cough, Valsalva, or sneeze
- Headache triggered by exercise
- Orthostatic headache
- Symptoms suggestive of giant cell arteritis
- Symptoms and signs of acute narrow-angle glaucoma
- Substantial change in the characteristics of their headache

NICE guidance also states that further investigation or referral may be warranted for people with new-onset headache and:

- Compromised immunity
- Age under 20 years and a history of malignancy

- A history of malignancy known to metastasize to the brain
- Vomiting without other obvious cause

Note: The NICE guidance is currently being reviewed and updated.

7. Toward Optimized Practice. (2012). Guideline for primary care management of headache in adults. Edmonton (AB): Toward Optimized Practice.

Citation 7 is a guideline from Toward Optimized Practice and the Institute of Health Economics in Alberta. According to these guidelines neuroimaging should not be obtained for common primary headache disorders or to reassure patients. They state that neuroimaging should be obtained:

- Emergently for:
  - Thunderclap headache
  - Headache with meningismus
  - Papilloedema with altered level of consciousness or focal signs
  - Acute angle-closure glaucoma
- Urgently for:
  - Signs of systemic illness in a patient with new onset headache
  - New headache in people over age 50 with other symptoms suggestive of temporal arteritis
  - Papilloedema without focal signs
  - Elderly patients with new headache and subacute cognitive change
- In the outpatient setting for:
  - Atypical headaches and change in headache pattern
  - Unexplained focal signs
  - Unusual headache precipitants
  - Unusual aura symptoms
  - Cluster headache and other uncommon primary headache syndromes
  - Late onset headache (after age 50)

8. van Ravesteijn, H., vanDijk, I., Darmon, D., vandeLaar, F., Lucassen, P., Hartman, T. O., vanWeel, C. & Speckens, A. (2012). The reassuring value of diagnostic tests: a systematic review. *Patient Education and Counseling, 86*(1), 3-8. DOI: 10.1016/j.pec.2011.02.003.

Citation 8 is a SR and narrative synthesis of studies pertaining to reassurance provided by diagnostic tests. They include one RCT of MRI brain to provide reassurance for patients with

chronic headaches which concluded that while anxiety levels improve at 3 months that there is no difference at 1 year.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "headache" and "imaging" or "neuroimaging." Searches of core sources were limited to citations published since 2010.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published since 2010.

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

PET Scanning for Breast Cancer – 2015 Rescanning Summary

Subcommittee: Health Technology Assessment Subcommittee (HERC approved August 2013)

HTAS Recommendation: Reaffirm the existing coverage guidance and reconsider the need to update it during the regular two-year review cycle.

Bottom Line: While new evidence may offer refined estimates of the diagnostic performance of PET, there remains a paucity of data regarding its effects on treatment plans or clinical outcomes.

Coverage Recommendation (Box Language)

PET scanning is not recommended for coverage in initial staging of breast cancer at low risk for metastasis (asymptomatic individuals with newly identified ductal carcinoma in situ, or clinical stage I or II disease).

PET scanning is not recommended for coverage as a modality to monitor response to treatment of breast cancer.

PET scanning is not recommended for coverage for surveillance testing for asymptomatic individuals who have been treated for breast cancer with curative intent.

Scope Statement

Population description	Adults with early stage breast cancer (DCIS, stage I, or stage II) or who have been treated for breast cancer with curative intent *Population scoping notes: None*
Intervention(s)	PET CT for initial staging, surveillance, or monitoring response to treatment *Intervention exclusions: None*
Comparator(s)	Usual care (including axillary lymph node dissection [with or without sentinel lymph node biopsy], CT and radionuclide scintigraphy), MRI
Outcome(s) (up to five)	**Critical:** All-cause mortality, cancer-specific mortality **Important:** Progression-free survival, false positive tests, quality of life *Considered but not selected for GRADE table: None*

Key questions	1. What is the comparative effectiveness of PET CT in early stage breast cancer or breast cancer treated with curative intent in improving patient important outcomes for staging, monitoring response, or surveillance? 2. What are the harms (including false positive tests, radiation exposure) of PET in early stage breast cancer or breast cancer treated with curative intent? Contextual Questions 1. How often do the results of PET CT after breast cancer diagnosis lead to changes in the surgical or non-surgical treatment plan?

Original Evidence Sources

Choosing Wisely®, the ABIM Foundation. (2012). Lists. Retrieved from http://choosingwisely.org/?page_id=13

HAYES, Inc. (2010). *Positron emission tomography (PET) and combined positron emission tomography-computed tomography (PET-CT) for breast cancer staging*. Lansdale, PA: HAYES, Inc.

National Collaborating Centre for Cancer (NCCC). (2009). *Advanced breast cancer: diagnosis and treatment – Evidence review*. Cardiff, Wales: National Collaborating Centre for Cancer. Retrieved from http://guidance.nice.org.uk/index.jsp?action=download&o=44046

Pennant, M., Takwoingi, Y., Pennant, L., Davenport, C., Fry-Smith, A., Eisinga, A., … Hyde, C. (2010). A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence. *Health Technology Assessment, 14*(50).

Schnipper, L. E., Smith, T. J., Raghavan, D., Blayney, D. W., Ganz, P. A., ... Wollins, D. S. (2012). American Society of Clinical Oncology identified five key opportunities to improve care and reduce costs: The top five list for oncology. *Journal of Clinical Oncology*, *30*(14), 1715-1724.

Scanning Results

1. Annunziata, S., Caldarella, C., & Treglia, G. (2014). Cost-effectiveness of Fluorine-18-Fluorodeoxyglucose positron emission tomography in tumours other than lung cancer: a systematic review. *World Journal of Radiology, 6*(3): 48-55. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3986420/

Citation 1 is a SR of cost-effectiveness studies of PET for cancers other than lung cancers. It includes 2 studies on the cost-effectiveness of PET for breast cancer, though these studies were done in Canada and the United Kingdom. In the Canadian study, PET was found to be cost-saving compared with axillary LND in newly diagnosed early stage breast cancer. In the UK study, a strategy of initial PET scanning dominated initial sentinel lymph node biopsy for new diagnoses of early stage breast cancer. However, these economic analyses may be too indirect to influence new coverage guidance.

2. Auguste P, Barton P, Hyde C, Roberts T. E. An economic evaluation of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence. *Health Technol Assess 2011;15*(18). DOI: 10.3310/hta15180.

Citation 2 is an economic evaluation of PET for the diagnosis of recurrent breast cancer. The perspective was that of the British NHS. The incremental cost effectiveness ratio for PET was 31,000 GBP per QALY. This economic analysis would probably be too indirect to influence new coverage guidance.

3. Brennan, M. E. & Houssami, N. (2012). Evaluation of the evidence on staging imaging for detection of asymptomatic distant metastases in newly diagnosed breast cancer. *Breast*, *21*(2), 112-123. DOI: 10.1016/j.breast.2011.10.005.

Citation 3 is a SR of 22 studies examining various modalities for the detection of asymptomatic distant metastases in newly diagnosed breast cancer. While PET has very good operating characteristics, the authors note that there is a low prevalence of distant metastatic disease in newly diagnosed early stage breast cancer (median prevalence of 0.2% to 1.2%) and that there is likely a selection bias in the literature they reviewed.

4. Bruening, W., Uhl, S., Fontanarosa, J., Reston, J., Treadwell, J., & Schoelles, K. (2012). Noninvasive diagnostic tests for breast abnormalities: Update of a 2006 review. Comparative Effectiveness Review No. 47. (Prepared by the ECRI Institute Evidence-based Practice Center under Contract No. 290-02-0019.) AHRQ Publication No. 12-

EHC014-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2012. Retrieved from www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Citation 4 is an AHRQ review of various non-invasive imaging modalities for evaluation of abnormalities identified on routine screening. Based on 7 studies of PET, the summary sensitivity and specificity were 83% and 74% respectively. The authors conclude that the use of PET in this circumstance would not generally change management unless the pre-test probability of breast cancer was less than 5%. Furthermore, B-mode grayscale ultrasound and MRI appear to be more accurate than PET.

5. Clark, E. E. (2011). Positron emission tomography (PET) scanning in malignancy. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University. Retrieved from https://www.medclearinghouse.org/index.cfm?fuseaction=file.secure&loc=5&file=/topicfile_478.pdf.

Citation 5 is a MED report on PET for malignancy. With regard to its use in breast cancer, the report concludes that "PET is insufficiently accurate to be used instead of surgery for detection of cancer in breast masses or for axillary lymph node staging. MRI appears to be more accurate than PET for detection of recurrence or distant metastases. PET may be useful for identifying patients with advanced cancer who are or are not responding to treatment."

6. Cooper, K. L., Meng, Y., Harnan, S., Ward, S. E., Fitzgerald, P., Papaioannou, D.,…, &Lorenz, E. (2011). Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: Systematic review and economic evaluation. *Health Technology Assessment, 15*(4). DOI: 10.3310/hta15040.

Citation 6 is a SR and economic evaluation of PET, MRI, and various lymph node sampling techniques for the diagnosis of axillary lymph node metastases. In 26 included studies of PET, the summary sensitivity and specificity of PET were 63% and 94% respectively. PET performance was diminished for detection of small axillary metastases. In the cost-effectiveness analysis, MRI was the dominant strategy, though this UK economic analysis may be too indirect to influence new coverage guidance.

7. Deng, S. M., Zhang, W., Zhang, B., & Wu, Y. W. (2014). Assessment of tumor response to chemotherapy in patients with breast cancer using (18)F-FLT: a meta-analysis. *Chinese Journal of Cancer Research,* 26(5): 517-524. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4220254/

Citation 7 is a MA of 4 studies examining the use of PET for assessing response to chemotherapy for patients with breast cancer. The reference standard was histopathologic, clinical, or radiologic follow-up at 6 months. The summary sensitivity and specificity of PET for assessing response to chemotherapy were 77% and 68% respectively. The study did not assess clinical outcomes or changes to treatment plans as a result of PET.

8. Gold, L. S., Lee, C. I., Devine, B., Nelson, H., Chou, R., Ramsey, S., & Sullivan, S. D. (2014). Imaging techniques for treatment evaluation for metastatic breast cancer [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Oct. (Technical Briefs, No. 17.) Retrieved from: http://www.ncbi.nlm.nih.gov/books/NBK253155/

Citation 8 is an AHRQ review of imaging modalities to assess response to treatment for patients with metastatic breast cancer. The authors conclude that "while some early evidence suggests that the metabolic response assessed by FDG-PET/CT after initial cycles of chemotherapy may be predictive of response to treatment among metastatic breast cancer patients, more rigorous research is needed before definitive conclusions can be reached."

9. Hong, S., Li, J., & Wang, S. (2013). FDG PET-CT for diagnosis of distant metastases in breast cancer patients: a meta-analysis. *Surgical Oncology, 22*(2): 139-143. doi:10.1016/j.suronc.2013.03.001.

Citation 9 is a MA of 8 studies of PET for evaluation of distant metastatic disease in patients with breast cancer. The summary sensitivity and specificity of PET were 97% and 95% respectively. Changes in treatment plan or clinical outcomes were not reported.

10. MacDonald, S. M., Haffty, B. G., Harris, E. E., Arthur, D. W. , Bailey, L., Bellon, J. R., & Moran M. S. (2011). ACR Appropriateness Criteria® locally advanced breast cancer. [online publication]. Reston (VA): American College of Radiology (ACR). Retrieved from http://www.guideline.gov/content.aspx?id=32632

Citation 10 is ACR Appropriateness Criteria for various imaging modalities in patients with locally advanced breast cancer. The very specific scenarios used in this report would likely not be generalizable to an updated coverage guidance.

11. Mghanga, F. P., Lan, X., Bakari, K. H., Li C., & Zhang Y. (2013). Fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography in monitoring the response of breast cancer to neoadjuvant chemotherapy: a meta-analysis. *Clinical Breast Cancer, 13*(4): 271-279. DOI: 10.1016/j.clbc.2013.02.003.

Citation 11 is a SR and MA of 15 studies of PET for assessing the response to neoadjuvant chemotherapy. The summary sensitivity and specificity of PET for distinguishing responders from non-responders were 80% and 79% respectively. Changes in treatment plan or clinical outcomes were not reported.

12. Moy, L., Newell, M. S., Bailey, L., Barke, L. D., Carkaci, S., D'Orsi, C., … Mahoney M. C. (2014). ACR Appropriateness Criteria® stage I breast cancer: initial workup and surveillance for local recurrence and distant metastases in asymptomatic women [online publication]. Reston (VA): American College of Radiology (ACR). Retrieved from http://www.guideline.gov/content.aspx?id=48278

Citation 12 is ACR Appropriateness Criteria for various imaging modalities in the initial work-up or surveillance for asymptomatic local recurrence or distant metastases in patients with stage I breast cancer. For all proposed indications, PET receives a rating of 1 or 2 which is "usually not appropriate."

13. Pan, L., Han, Y., Sun, X., Liu, J., & Gang, H. (2010). FDG-PET and other imaging modalities for the evaluation of breast cancer recurrence and metastases: a meta-analysis. *Journal of Cancer Research and Clinical Oncology, 136*(7): 1007-1022. DOI: 10.1007/s00432-009-0746-6.

Citation 13 is a SR and MA of 42 studies of imaging modalities for evaluation of breast cancer recurrence or metastases. The summary sensitivity and specificity of PET were 95% and 86% respectively. MRI was the only imaging modality with better operating characteristics. Changes in treatment plan or clinical outcomes were not reported.

14. Wang, Y., Zhang, C., Liu, J., & Huang, G. (2012). Is 18F-FDG PET accurate to predict neoadjuvant therapy response in breast cancer? A meta-analysis. *Breast Cancer Research and Treatment, 131*(2): 357-369. DOI: 10.1007/s10549-011-1780-z.

Citation 14 is a SR and MA of 19 studies examining the use of PET for evaluation of response to neoadjuvant chemotherapy. Compared to a reference standard of histopathologic response in primary breast cancers, the summary sensitivity and specificity of PET were 84% and 66% respectively. Changes in treatment plan or clinical outcomes were not reported.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "coronary computed tomography" and "coronary CT angiography." Searches of core sources were limited to citations published after 2011.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2011.

Searches for clinical practice guidelines were limited to those published since 2012. A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Self-Monitoring of Blood Glucose for Type 1 & Type 2 Diabetes – 2015 Rescanning Summary

Subcommittee: Health Technology Assessment Subcommittee (HERC approved December 2013)

HTAS Recommendation: Reaffirm the existing coverage guidance and reconsider the need to update it during the regular two-year review cycle.

Bottom Line: Several new systematic reviews and meta-analyses have examined the effects of SMBG for patients with T2DM on non-insulin therapies. These reviews all suggest a small improvement in A1c (0.2% to 0.3%) with use of SMBG. Evidence of clinical outcomes is lacking. Available guidelines support the use of SMBG in patients on multiple daily insulin injections and in pregnant women.

Coverage Recommendation (Box Language)

For patients with type 1 diabetes and those with type 2 diabetes using multiple daily insulin injections, home blood glucose monitors and related diabetic supplies are recommended for coverage (*strong recommendation*).

For patients with type 2 diabetes not requiring multiple daily insulin injections, fifty test strips and related supplies are recommended for coverage at the time of diagnosis (*weak recommendation*). For those who require diabetic medication that may result in hypoglycemia, up to 50 test strips per 90 days are recommended for coverage (*weak recommendation*). If there is an acute change in glycemic control or active diabetic medication adjustment, an additional 50 strips are recommended for coverage (*weak recommendation*).

For all diabetic patients who are prescribed diabetic test strips, a structured education and feedback program for self-monitoring of blood glucose is recommended for coverage (*strong recommendation*).

Note: This guidance does not apply to pregnant women.

Scope Statement

Population description	Children, adolescents, and adults with type 2 diabetes mellitus who are not using multiple daily insulin injections (MDII) *Population scoping notes: None*

Intervention(s)	Self-monitoring of blood glucose (SMBG), with or without structured education and feedback programs. *Intervention exclusions: None*
Comparator(s)	No routine monitoring using SMBG, periodic monitoring of HbA1c
Outcome(s) (up to five)	**Critical:** Severe morbidity (e.g. microvascular and macrovascular complications), severe hypoglycemia[1] **Important:** Quality-of-life, change in HbA1c, hyperosmolar hyperglycemic state *Considered but not selected for GRADE table: Hospitalizations, emergency department visits, all-cause mortality.*
Key questions	1. What is the effectiveness of SMBG in improving outcomes in children, adolescents, and adults with type 2 diabetes mellitus who are not using multiple daily insulin injections (MDII)? 2. What is the evidence of harms associated with SMBG in this population? 3. Is there evidence of differential effectiveness of SMBG based on: a. Type of treatment (i.e. diet and exercise, oral antidiabetic agents, basal insulin, non-insulin injectables) b. Frequency of testing c. Degree of glycemic control at baseline d. Association with a structured education and feedback program 4. What are appropriate quantities of testing supplies for this population, and what factors should trigger allowances for additional supplies (e.g. infection, driving, etc.)
Special Considerations – Rescanning	We will not search the literature on people with Type I diabetes or Type II diabetes with multiple daily insulin injections, as these are well-established and had a strong recommendation in the last coverage guidance.

[1] "An event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions." (ADA Workgroup on Hypoglycemia, 2005)

Original Evidence Sources

Gerrity, M., Kriz, H., & Little, A. (2010). *Self-monitoring of blood glucose for type 1 and type 2 diabetes*. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University.

Key Sources Cited In MED Report

Clar, C., Barnard, K., Cummins, E., Royle, P., & Waugh, N. (2010). Self-monitoring of blood glucose in type 2 diabetes: Systematic review. *Health Technology Assessment, 14*(12), 1-140. DOI: 10.3310/hta14120.

The Diabetes Control and Complications Trial Research Group. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *New England Journal of Medicine, 329*(14), 977- 986. DOI: 10.1056/NEJM199309303291401.

Scanning Results

1. American Diabetes Association. (2012). Standards of medical care in diabetes—2012. *Diabetes Care, 35*(Suppl 1), S11-63.

Citation 1 is a clinical practice guideline from the American Diabetes Association. The ADA offers the following recommendations regarding SMBG:

- SMBG should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy. (B)
- For patients using less-frequent insulin injections, noninsulin therapies, or medical nutrition therapy (MNT) alone, SMBG may be useful as a guide to management. (E)
- To achieve postprandial glucose targets, postprandial SMBG may be appropriate. (E)
- When prescribing SMBG, ensure that patients receive initial instruction in, and routine follow-up evaluation of, SMBG technique and their ability to use data to adjust therapy. (E)

B recommendations are based on data from well-conducted cohort studies. E recommendations are based on expert opinion/consensus.

2. Breland, J. Y., McAndrew, L. M., Burns, E., Leventhal, E. A., & Leventhal, H. (2013). Using the common sense model of self-regulation to review the effects of self-monitoring of blood glucose on glycemic control for non-insulin-treated adults with type 2 diabetes. *Diabetes Educator, 39*(4), 541-59.

Citation 2 is a SR of 26 studies of SMBG for adults with T2DM on non-insulin therapies. The studies were published between 2007 and 2011. Eleven of the included trials were RCTs. These trials were heterogeneous and the results were mixed. Some trials found that SMBG + education resulted in improvement in A1c, but other trials found that education alone achieved similar reductions. Clinical outcomes are not reported.

3. Canadian Agency for Drugs and Technologies in Health (CADTH). (2013). *Blood glucose monitors and test strips: a review of the comparative clinical evidence and cost-effectiveness — an update*. Ottawa: CADTH.

Citation 3 is a comparative study of the accuracy of different glucometers. It would not be relevant to an update of this coverage guidance.

4. Farmer, A. J., Perera, R., Ward, A., Heneghan, C., Oke, J., Barnett, A. H., … O'Malley, S. (2012). Meta-analysis of individual patient data in randomised trials of self monitoring of blood glucose in people with non-insulin treated type 2 diabetes. *British Medical Journal, 344*, e486.

Citation 4 is a patient-level meta-analysis of the effects of SMBG for non-insulin treated adults with T2DM. The authors conclude that SMBG is not associated with clinically meaningful improvements in diabetic control in this population.

5. Hou, Y. Y., Li, W., Qiu, J. B., & Wang, X. H. (2014). Efficacy of blood glucose self-monitoring on glycemic control in patients with non-insulin-treated type 2 diabetes: a meta-analysis. *International Journal of Nursing Sciences, 1*(2), 191-195.

Citation 5 is a SR and MA of 7 RCTs of SMBG in non-insulin treated adults with T2DM. The authors conclude that SMBG in conjunction with diabetic education results in improvements in A1c of 0.42%. SMBG without diabetic education did not improve A1c.

6. Kesavadev, J., Sadikot, S., Wangnoo, S., Kannampilly, J., Saboo, B., Aravind, S. R., … Vishwanathan V. (2014). Consensus guidelines for glycemic monitoring in type 1/type 2 & GDM. *Diabetes & Metabolic Syndrome, 8*(3), 187-95.

Citation 6 is a clinical practice guideline from Diabetes India. It provides 13 recommendations regarding the use of SMBG. All but one of the recommendations is based on expert opinion and the remaining recommendation is based on observational studies.

7. Malanda, U. L., Welschen, L. M. C., Riphagen, I. I., Dekker, J. M., Nijpels, G., Bot, S. D. M. (2012). Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. Cochrane Database of Systematic Reviews 2012, Issue 1. A rt. No.: CD005060. DOI: 10.1002/14651858.CD005060.pub3.

Citation 7 is a Cochrane review of SMBG for patients with T2DM not on insulin. It includes 12 RCTs spanning more than 3,200 patients. The authors conclude that in this population, SMBG results in slight improvements in A1c at 6 months, but these improvements wane by 12 months. Furthermore, SMBG was not associated with improved patient satisfaction or health-related quality of life.

8. McIntosh, B., Yu, C., Lal, A., Chelak, K., Cameron, C., Singh, S. R., & Dahl, M. (2010). Efficacy of self-monitoring of blood glucose in patients with type 2 diabetes mellitus managed without insulin: a systematic review and meta-analysis. *Open Medicine, 4*(2), e102-e113.

Citation 8 is a SR and MA of the effects of SMBG in patients with T2DM on oral antidiabetic agents. They conclude that SMBG is associated with small improvements in A1c (0.25%) at 6 months. SMBG appeared to have no effect on quality of life, hypoglycemia, long-term complications of DM2, or mortality.

9. Minet, L., Moller, S., Vach, W., Wagner, L., & Henriksen, J. E. (2010). Mediating the effect of self-care management intervention in type 2 diabetes: a meta-analysis of 47 randomised controlled trials. *Patient Education and Counseling, 80*(1), 29-41.

Citation 9 is a SR and MA of over 40 trials of self-care management interventions in T2DM. It does not explicitly address the use of SMBG.

10. Moy, F. M., Ray, A., & Buckley, B. S. (2014). Techniques of monitoring blood glucose during pregnancy f or women with pre-existing diabetes. *Cochrane Database of Systematic Reviews*, Issue 4. Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009613.pub2/epdf

Citation 10 is a Cochrane review of SMBG for pregnant women with pre-existing diabetes. Only 2 of the included studies compared SMBG with usual care. Both studies were small and published in the early 1980s. There were no significant differences in maternal or fetal outcomes in these studies.

11. NHS. (2013). *When is self monitoring of blood glucose recommended in type 2 diabetes*? Regional Drug and Therapeutics Centre. Retrieved from http://www.medicinesresources.nhs.uk/GetDocument.aspx?pageId=760035

Citation 11 summarizes NICE guidance on SMBG for patients with T2DM. The key recommendations are:

Self Monitoring of blood glucose should only be offered as an integral part of diabetes self-management education, and should be available to:

- Those on insulin treatment
- Those on oral glucose lowering medications who may be at risk of hypoglycemia
- Assess the impact of lifestyle and medication changes on blood glucose control
- Monitor changes during acute inter current illness
- Ensure safety during activities such as driving

Therefore patients with type 2 diabetes who are controlled by diet, metformin or glitazones should not routinely be offered SMBG.

12. NICE. (2015). *Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period.* London: NICE. Retrieved from http://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-its-complications-from-preconception-to-the-postnatal-period-51038446021

Citation 12 is a NICE guideline on the use of SMBG in pregnancy. It recommends that SMBG should be used in a variety of scenarios, including women with pre-existing diabetes and for women with a history of gestational diabetes in a prior pregnancy.

13. St John, A., Davis, W. A., Price, C. P., & Davis, T. M. (2010). The value of self-monitoring of blood glucose: a review of recent evidence. *Journal of Diabetes and Its Complications, 24*(2), 129-141.

Citation 13 is a SR and MA of 6 RCTs of SMBG for patients with T2DM treated with non-insulin therapies. SMBG was associated with a small improvement in A1c (0.22%). They note that this is consistent with the findings of observational trials.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "self monitor glucose." Searches of core sources were limited to citations published after 2009.

The core sources searched included:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Health Technology Assessment (HTA) program
BMJ Clinical Evidence
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Interscience)
Hayes, Inc.
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2008.

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Centers for Disease Control and Prevention (CDC) – Community Preventive Services
Institute for Clinical Systems Improvement (ICSI)
National Guidelines Clearinghouse
New Zealand Guidelines Group
NICE
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Treatment of Attention Deficit/Hyperactivity Disorder in Children – 2015 Rescanning Summary

Subcommittee: Evidence-based Guidelines Subcommittee (December 2013)

EbGS Recommendation: Consider development of a new coverage guidance to update this topic upon completion of a pending NICE report.

Bottom Line: Given the vast number of systematic reviews that have been published on the treatment of attention deficit/hyperactivity disorder in children in recent years, the Subcommittee may wish to delay reviewing this coverage guidance until the NICE guideline is published in early 2016.

Coverage Recommendation (Box Language)

Children under Age 6

For children under 6 diagnosed with disruptive behavior disorders[1], including those at risk for ADHD, specific parent behavior training[2] is recommended for coverage as first-line therapy *(strong recommendation)*.

Pharmacotherapy[3] is recommended for coverage as a second line therapy *(weak recommendation).*

Provider consultation with teachers is recommended for coverage *(weak recommendation).*

Children Age 6 and Over

For children 6 and over who are diagnosed with ADHD[1], pharmacotherapy[3] alone *(weak recommendation)* or pharmacotherapy[3] with psychosocial/behavioral treatment *(strong recommendation)* are recommended for coverage.

Provider consultation with teachers is recommended for coverage *(weak recommendation).*

[1]*Children with comorbid mental health conditions may require additional or different treatments that are not addressed in this guidance.*

[2]*Effective studied types of parent behavior training include: Triple P (Positive Parenting of Preschoolers) Program, Incredible Years Parenting Program, Parent-Child Interaction Therapy and New Forest Parenting Program. The term "parent" refers to the child's primary care givers, regardless of biologic or adoptive relationship.*

[3]*Limited to medications that are FDA-approved for the condition.*

Scope Statement

Population description	Children 6 years of age or older diagnosed with ADHD or children under 6 years of age deemed at-risk for ADHD *Population scoping notes:* None
Intervention(s)	Parent behavior training, teacher consultation, pharmacotherapy (methylphenidate, amphetamine salts, non-stimulant medications, atypical antipsychotics), other pharmacologic treatments, psychosocial and behavioral interventions, dietary supplements, complementary and alternative medicine (CAM) *Intervention exclusions:* Changes in diet
Comparator(s)	Usual care, no intervention
Outcome(s) (up to five)	**Critical:** Academic achievement, measures of social functioning **Important:** Measures of impulsiveness, grade retention, growth restriction *Considered but not selected for GRADE table:* Measures of inattention, overactivity, non-specific harms
Key questions	1. What is the effectiveness of pharmacologic, behavioral, and psychosocial interventions for children with ADHD? a. Does effectiveness vary based on patient characteristics, including mental health comorbidities? 2. Is there comparative effectiveness evidence for interventions for children with ADHD? 3. What is the effectiveness of interventions for children under 6 years of age deemed at-risk for ADHD? 4. What is the evidence of harms associated with the interventions for ADHD in children? a. Do harms vary based on patient characteristics, including mental health comorbidities?

Original Evidence Sources

American Academy of Pediatrics (AAP). (2011). Supplemental information. Implementing the key action statements: An algorithm and explanation for process of care for the evaluation, diagnosis, treatment, and monitoring of ADHD in children and adolescents. *Pediatrics,* SI1-SI21. Retrieved December 5, 2012, from http://pediatrics.aappublications.org/content/128/5/1007/suppl/DC1

Charach, A., Dashti, B., Carson, P., Booker, L., Lim, C.G., Lillie, E., et al. (2011). *Attention deficit hyperactivity disorder: Effectiveness of treatment in at-risk preschoolers; long-term effectiveness in all ages; and variability in prevalence, diagnosis, and treatment. Comparative effectiveness review no. 44.* (Prepared by the McMaster University Evidence-based Practice Center under Contract No. MME2202 290-02- 0020.) AHRQ Publication No. 12-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Scanning Results (reviewed for applicability, methodologic quality not assessed)

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5. Canadian Agency for Drugs and Technologies in Health (CADTH). (2013). *Abuse and misuse potential of drugs for attention deficit/hyperactivity disorder: A review of the clinical evidence.* Ottawa: CADTH.
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8. Carson, S., Pettinari, C., Thielke, A., & King, V. (2014). *Non-pharmacological Treatments for ADHD.* Portland, OR: Center for Evidence-based Policy, Oregon, Health & Science University.

Included Citations

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c. Evans, S. W., Owens, J. S., & Bunford, N. (2013). Evidence-based psychosocial treatments for children and adolescents with attention-deficit/hyperactivity disorder. *Journal of Clinical Child & Adolescent Psychology, 43,* 527-551.
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g. Hodgson, K., Hutchinson, A. D., & Denson, L. (2014). Nonpharmacological treatments for ADHD: A meta-analytic review. *Journal of Attention Disorders, 1*8(4), 275-272. doi: 10.1177/1087054712444732.
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trials across multiple outcome domains. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(8), 835-847, e1-5.

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19. Ghanizadeh, A. (2015). A systematic review of reboxetine for treating patients with attention deficit hyperactivity disorder. *Nordic Journal of Psychiatry*, *69*(4), 241-248.
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21. Grassmann, V., Alves, M. V., Santos-Galduroz, R. F., & Galduroz, J. C. (2014). Possible cognitive benefits of acute physical exercise in children with ADHD: a systematic review. *Journal of Attention Disorders*, epub.
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26. Keen, D., & Hadjikoumi, I. (2011). ADHD in children and adolescents. *BMJ Clinical Evidence, 02*, 312-346.

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36. Pringsheim, T., & Steeves, T. (2011). Pharmacological treatment for attention deficit hyper activity disorder (ADHD) in children with comorbid tic disorders. *Cochrane Database of Systematic Reviews,* Issue 4.

37. Punja, S., Zorzela, L., Hartling, L., Urichuk, L., & Vohra, S. (2013). Long-acting versus short-acting methylphenidate for paediatric ADHD: a systematic review and meta-analysis of comparative efficacy. *BMJ Open, 3*(3), e002312.

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Summary

A large volume of studies have been published since this coverage guidance was developed. An update to the 2008 NICE guideline on attention deficit hyperactivity disorder is expected to be published in early 2016. In addition, the Agency for Healthcare Research and Quality is in the process of updating the 2011 report.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "attention deficit hyperactivity disorder." Searches of core sources were limited to citations published after 2010 (last search date of original evidence sources).

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Health Technology Assessment (HTA) program
- *BMJ Clinical Evidence*
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- Hayes, Inc.
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2013 due to the large amount of information identified in the core source search.

Searches for clinical practice guidelines were limited to those published since 2010 (last search date of coverage guidance). A search for relevant clinical practice guidelines was also conducted, using the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- Institute for Clinical Systems Improvement (ICSI)
- National Guidelines Clearinghouse
- New Zealand Guidelines Group
- NICE
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, , did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Vertebroplasty, Kyphoplasty, Sacroplasty – 2015 Rescanning Summary

Subcommittee: Health Technology Assessment Subcommittee (HERC approved May 2013)

Recommendation: *HTAS did not review this due to a staff error. Staff and HTAS leadership recommend that HERC reaffirm the existing coverage guidance and reconsider the need to update it during the regular two-year review cycle.*

Bottom Line: Additional evidence supports that vertebroplasty and kyphoplasty may offer improved pain relief at up to 1 year following acute osteoporotic compression fractures when compared with optimal medical treatment. However, in studies that compare these percutaneous procedures with sham procedures that include local anesthesia, the benefits are not apparent. Clinical guidelines generally support the use of kyphoplasty and vertebroplasty for intractable pain from osteoporotic compression fractures despite optimal medical treatment. There is limited additional evidence regarding sacroplasty for sacral insufficiency fractures.

Coverage Recommendation (Box Language)

Vertebroplasty and kyphoplasty should be covered under the following circumstances:

1. The patient is hospitalized under inpatient status due to pain that is primarily related to a well-documented acute fracture, and
2. The severity of the pain prevents unassisted ambulation, and
3. The pain is not adequately controlled with oral or transcutaneous medication.

The patient must have failed an appropriate trial of conservative management.

Vertebroplasty and kyphoplasty should not be covered under other circumstances.

Sacroplasty should not be covered.

Note: This coverage guidance does not address vertebral fractures related to malignancy.

Scope Statement

Population description	Adults with acute or chronic vertebral compression or sacral insufficiency fractures *Population scoping notes: None*
Intervention(s)	Percutaneous vertebral and sacral procedures *Intervention exclusions: None*
Comparator(s)	Open spinal surgical procedures, sham/placebo surgery, medical therapy (including non-pharmacologic interventions like physical therapy or acupuncture)
Outcome(s) (up to five)	Critical: All-cause mortality, short- and long-term improvement in function Important: Short- and long-term improvements in pain or quality of life, recurrent fracture, clinically significant embolization *Considered but not selected for GRADE table: Length of stay*
Key questions	1. What is the comparative effectiveness of percutaneous interventions for vertebral compression or sacral insufficiency fractures? 2. What are the harms of percutaneous interventions for vertebral compression or sacral insufficiency fractures?

Original Evidence Source

Washington State Health Care Authority Health Technology Assessment Program. (2010). *Vertebroplasty, kyphoplasty and sacroplasty: Health technology assessment.* Olympia, WA: Health Technology Assessment Program. Retrieved from http://www.hta.hca.wa.gov/documents/vks_final_report.pdf

Scanning Results

1. McConnell, C. T. Jr., Wippold, F. J. II, Ray, C. E. Jr., Weissman, B. N., Angevine, P. D., Fries, I. B., … Rubin, D. A., Expert Panels on Neurologic Imaging, Interventional Radiology and Musculoskeletal Imaging. (2013). *ACR Appropriateness Criteria® management of vertebral*

compression fractures. Reston (VA): American College of Radiology. Retrieved from https://acsearch.acr.org/docs/70545/Narrative/

Citation 1 is an American College of Radiology Appropriateness Criteria guideline. Depending on the clinical scenario, the recommendations for vertebroplasty, kyphoplasty, and sacroplasty vary from "usually not appropriate" to "usually appropriate."

2. Baerlochr, M. O., Saad, W. E., Dariushnia, S., Barr, J. D., McGraw, J. K., Nikolic, B., & Society of Interventional Radiology Standards of Practice Committee. (2014). Quality improvement guidelines for percutaneous vertebroplasty. *Journal of Vascular and Interventional Radiology, 25*(2), 165-70.

Citation 2 is a quality improvement guideline from the Society of Interventional Radiology. It offers indications and contraindications for vertebroplasty, but the degree to which these recommendations are evidence-based in unclear.

3. Barr, J. D., Jensen, M. E., Hirsch, J. A., McGraw, J. K., Barr, R. M., Brook, A. L., … Cardella, J. F. (2014). Position statement on percutaneous vertebral augmentation: A consensus statement developed by the Society of Interventional Radiology (SIR), American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), American College of Radiology (ACR), American Society of Neuroradiology (ASNR), American Society of Spine Radiology (ASSR), Canadian Interventional Radiology Association (CIRA), and the Society of NeuroInterventional Surgery (SNIS). *Journal of Vascular and Interventional Radiology, 25*(1), 171-81.

Citation 3 is a multi-society clinical practice guideline pertaining to vertebroplasty. It recommends vertebroplasty as an "appropriate therapy for treatment of painful VCFs refractory to nonoperative medical therapy and for vertebrae weakened by neoplasia…"

4. Bouza, C., Lopez-Cuadrado, T., Almendro, N., & Amate, J. M. (2015). Safety of balloon kyphoplasty in the treatment of osteoporotic vertebral compression fractures in Europe: a meta-analysis of randomized controlled trials. *European Spine Journal,* 24(4), 715-23.

Citation 4 is a systematic review and meta-analysis of RCTs examining the safety of balloon kyphoplasty. Serious complications are common, occurring in 10-20% of cases. Overall, the authors estimate 17 severe complications per 100 balloon kyphoplasties.

5. Buchbinder, R., Golmohammadi, K., Johnston, R. V., Owen, R. J., Homik, J., Jones, A., … Lambert, R. G. W. (2015). Percutaneous vertebroplasty for osteoporotic vertebral

compression fracture. *Cochrane Database of Systematic Reviews,* Issue 4. Art. No.: CD006349. DOI: 10.1002/14651858.CD006349.pub2.

Citation 5 is Cochrane Review of 11 RCTs and 1 quasi-randomized trial of vertebroplasty for osteoporotic compression fractures. The review concludes that "[b]ased upon moderate quality evidence, our review does not support a role for vertebroplasty for treating osteoporotic vertebral fractures in routine practice. We found no demonstrable clinically important benefits compared with a sham procedure and subgroup analyses indicated that results did not differ according to duration of pain ≤ 6 weeks versus > 6 weeks."

6. Chang, X., Lv, Y. F., Chen, B., Li, H. Y., Han, X. B., Yang, K., … Li, C. Q. (2015). Vertebroplasty versus kyphoplasty in osteoporotic vertebral compression fracture: a meta-analysis of prospective comparative studies. *International Orthopaedics*, *39*(3), 491-500.

Citation 6 is a systematic review and meta-analysis of prospective studies comparing vertebroplasty and kyphoplasty for osteoporotic compression fractures. Most outcomes were similar between the two procedures, including measures of pain relief, though it appears that cement leakage was slightly more common in vertebroplasty procedures.

7. HAYES, Inc. (2012). *Percutaneous kyphoplasty*. Lansdale, PA: HAYES, Inc.

Citation 7 is a Hayes review of kyphoplasty. They offer D2 ratings (insufficient evidence) of kyphoplasty for patients with medically refractory pain after osteoporotic or malignant vertebral compression fractures. This reflects the absence of high quality evidence of benefit and the possibility of serious harms.

8. HAYES, Inc. (2014). *Percutaneous sacroplasty for treatment of sacral insufficiency fractures*. Lansdale, PA: HAYES, Inc.

Citation 8 is Hayes review of sacroplasty. They offer a D2 rating (insufficient evidence) of sacroplasty for sacral insufficiency fractures. This is based on low-quality evidence from studies with serious methodologic flaws.

9. HAYES, Inc. (2012). *Percutaneous vertebroplasty*. Lansdale, PA: HAYES, Inc.

Citation 9 is a Hayes review of vertebroplasty. They offer a C rating (potential but unproven benefit) of vertebroplasty for osteoporotic compression fractures and a D2 rating (insufficient evidence) of vertebroplasty for malignant compression fractures.

10. Khan, O. A., Brinjikji, W., & Kallmes, D. F. (2014). Vertebral augmentation in patients with multiple myeloma: a pooled analysis of published case series. *American Journal of Neuroradiology, 35*(1), 207-10. DOI: 10.3174/ajnr.A3622.

Citation 10 is a pooled analysis of published case series of vertebral augmentation (vertebroplasty and kyphoplasty) in patients with fractures related to multiple myeloma. It appears that both procedures are effective at reducing pain at up to 1 year of follow-up.

11. Lange, A., Kasperk, C., Alvares, L., Sauermann, S., & Braun, S. (2014). Survival and cost comparison of kyphoplasty and percutaneous vertebroplasty using German claims data. *Spine, 39*(4), 318-326. DOI: 10.1097/BRS.0000000000000135.

Citation 11 is an observational study based on claims data from a single German health insurance fund. It concludes that in patients with osteoporotic vertebral compression fractures, kyphoplasty and vertebroplasty are associated with reduced risk of mortality over 5 years. This is a methodologically limited study that was funded by Medtronic.

12. NICE. (2013). Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for treating osteoporotic vertebral compression fractures. London: NICE. Retrieved from http://www.nice.org.uk/guidance/ta279/resources/guidance-percutaneous-vertebroplasty-and-percutaneous-balloon-kyphoplasty-for-treating-osteoporotic-vertebral-compression-fractures-pdf

Citation 12 is a NICE technology appraisal guidance on vertebroplasty and kyphoplasty for osteoporotic compression fractures. They recommend that "[p]ercutaneous vertebroplasty, and percutaneous balloon kyphoplasty without stenting, are recommended as options for treating osteoporotic vertebral compression fractures only in people: who have severe ongoing pain after a recent, unhealed vertebral fracture despite optimal pain management and in whom the pain has been confirmed to be at the level of the fracture by physical examination and imaging."

13. Song, D., Meng, B., Gan, M., Niu, J., Li, S., Chen, H., & Yang, H. (2015). The incidence of secondary vertebral fracture of vertebral augmentation techniques versus conservative treatment for painful osteoporotic vertebral fractures: a systematic review and meta-analysis. *Acta Radiologica*, *59*, 970-979.

Citation 13 is a systematic review and meta-analysis examining whether kyphoplasty or vertebroplasty for osteoporotic fractures is associated with secondary fractures. The

percutaneous procedures appear not to be associated with a greater risk of secondary fracture compared to conservative management.

14. Stevenson, M., Gomersall, T., Lloyd Jones, M., Rawdin, A., Hernández, M., Dias, S., … Rees, A. (2014). Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis. *Health Technology Assessment, 18*(17), 1-289. Retrieved from http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0017/114317/FullReport-hta18170.pdf

Citation 14 is an evidence review conducted by the National Health Service. The NHS concludes that "[f[or people with painful osteoporotic VCFs refractory to analgesic treatment, PVP and BKP perform significantly better in unblinded trials than OPM in terms of improving quality of life and reducing pain and disability. However, there is as yet no convincing evidence that either procedure performs better than OPLA [operative placebo with local anesthesia] with data from two high-quality trials…"

15. Tian, J., Xiang, L., Zhou, D., Fan, Q., & Ma, B. (2014). The clinical efficacy of vertebroplasty on osteoporotic vertebral compression fracture: a meta-analysis. *International Journal of Surgery, 12*(12), 1249-1253. DOI: 10.1016/j.ijsu.2014.10.027.

Citation 15 is a systematic review and meta-analysis of 5 RCTs of vertebroplasty for osteoporotic compression fractures. Compared with patients receiving optimal medical treatment, those who underwent vertebroplasty had significant improvements in pain score at up to 48 weeks of follow-up. There was no difference the occurrence of secondary fractures at adjacent vertebrae.

16. Xiao, H., Yang, J., Feng, X., Chen, P., Li, Y., Huang, C., … Chen, H. (2014). Comparing complications of vertebroplasty and kyphoplasty for treating osteoporotic vertebral compression fractures: a meta-analysis of the randomized and non-randomized controlled studies. *European Journal of Orthopaedic Surgery and Traumatology, 25*(Suppl 1), 77-85.

Citation 16 is a systematic review and meta-analysis of randomized and non-randomized trials comparing the complications of vertebroplasty vs kyphoplasty for osteoporotic compression fractures. Complication rates appear to be similar between procedures with the exception of cement leakage which is more common with vertebroplasty.

17. Zhang, Y. Z., Kong, L. D., Cao, J. M., Ding, W. Y., & Shen, Y. (2014). Incidence of subsequent vertebral body fractures after vertebroplasty. *Journal of Clinical Neuroscience*, *21*(8), 1292-1297.

Citation 17 is a systematic review and meta-analysis of four studies examining the risk of subsequent fractures after vertebroplasty. In the pooled analysis, vertebroplasty was not associated with an increased risk of new or adjacent vertebral fractures.

Appendix A. Methods

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms "vertebroplasty," "kyphoplasty," and "sacroplasty." Searches of core sources were limited to citations published after 2009 for kyphoplasty and Sacroplasty, and after 2013 for vertebroplasty.

The core sources searched included:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Health Technology Assessment (HTA) program
BMJ Clinical Evidence
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Interscience)
Hayes, Inc.
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE® (Ovid) search was conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of original evidence sources. The search was limited to publications in English published after 2009.

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Centers for Disease Control and Prevention (CDC) – Community Preventive Services
Institute for Clinical Systems Improvement (ICSI)
National Guidelines Clearinghouse
New Zealand Guidelines Group
NICE
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessment, or clinical practice guidelines.

Section 6.0

Coverage Guidances-EbGS

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: NITROUS OXIDE USE FOR LABOR PAIN MANAGEMENT

DRAFT for HERC/VbBS Meeting Materials 1/14/2016

HERC Coverage Guidance

Nitrous oxide for labor pain is recommended for coverage *(weak recommendation).*

Note: Definitions for strength of recommendation are provided in Appendix A GRADE-Informed Framework – Element Description.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are several elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by the Commission based on assessment of two independent reviewers from the Center for Evidence-based Policy. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of the Commission.

Coverage question: Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
Fetal/neonatal adverse effects *(Critical outcome)*	No significant differences in Apgar scores at 1 and 5 minutes, or umbilical cord gasses after birth when maternal N2O is compared to epidural anesthesia use. ●●●○ *(Moderate certainty, based on multiple RCTs and other studies with consistent findings)*	Use of N2O is likely to be cost-saving compared to epidural anesthesia. The cost of N2O is low. Use of N2O is associated with lower rates of assisted vaginal birth and cesarean delivery, and shorter length of stay on labor and delivery units.	High variability: Some women would want this additional option because of the reduced risk of caesarean section or assisted delivery. Concerns about harms would be mitigated because they could easily discontinue it and consider an epidural if adverse events occur or if analgesia is insufficient. Other	There is no specific CPT code for this service, other than an anesthesia code, so reimbursement to providers may require use of a non-specific code that may require manual review.
Mode of birth *(Critical outcome)*	Compared to women using epidural anesthesia, for those using N2O: 15 to 34 more women per 100 are likely to have an unassisted vaginal birth; 9 to 27 fewer women per 100 would experience assisted vaginal (forceps/vacuum) birth; and there would be about 6 fewer Cesarean births per 100 compared to those using epidural anesthesia for labor pain. ●●○○ *(Low certainty based on prospective cohort and cross sectional studies with consistent findings)*			

Coverage question: Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
Maternal adverse effects *(Important outcome)*	Women may experience unpleasant side effects when using N2O. (These data come from studies of women using N2O as the sole form of labor analgesia and are not compared to any other methods.) Nausea (0-28%), vomiting (0-14%), dizziness/lightheadedness (3-23%), and drowsiness/sleepiness (0-67%) were commonly reported side effects. Effects dissipated quickly when N2O use is stopped. ●●●○ (*Moderate certainty based on multiple RCTs and other studies with consistent findings*)		women may prefer epidural anesthesia because of its greater effect in reducing labor pain.	
Maternal satisfaction *(Important outcome)*	70 to 80% of women who used N2O said they would want to use it in a subsequent pregnancy compared to 45 to 88% of women who would request an epidural again. (These data come from studies where multiple labor pain management modalities are readily available and women using N2O or epidural were asked if they would want to use that method for a future birth.) ●●○○ (*Low certainty based on prospective cohort and cross-sectional studies with consistent findings*)			
Use of neuraxial (e.g., epidural) anesthesia *(Important outcome)*	When multiple pain management methods are available for women 13% to 79% will use N2O, compared to 34 to 42% who will select epidural anesthesia. There is no direct evidence on whether			

Coverage question: Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
	availability or use of N2O changes the use of neuraxial anesthesia. ●○○○ (*Very low certainty based on cross-sectional studies with consistent findings*)			
Rationale: On balance, there are potential benefits to the use of N2O and no serious harms to its use. Costs are low and variable maternal preferences argue for increased availability of N2O for management of labor pain. Coverage is recommended because of the potential benefits of fewer cesarean and assisted deliveries, the lack of significant harms, maternal preferences, and low costs. The recommendation is a weak recommendation because there are few studies available for benefit outcomes, and the external validity of the data and its applicability in U.S. settings is limited. The confidence in the quality of evidence for most outcomes is low to moderate certainty.				
Recommendation: Nitrous oxide for labor pain is recommended for coverage (*weak recommendation*).				

Note: GRADE-informed framework elements are described in Appendix A. Appendix B provides a GRADE Evidence Profile.

EVIDENCE OVERVIEW

Clinical background

Annually, approximately 45,000 births occur in Oregon (Oregon Health Authority, 2015) and childbirth pain is a major concern among women (Likis et al., 2012). Pain relief is most commonly delivered through epidural anesthesia in the United States, with 61% of women who had singleton births through vaginal delivery electing an epidural anesthesia (Centers for Disease Control and Prevention, 2011; Likis, et al., 2012). For women interested in other types of pain relief or in delaying the timing of an epidural, there are several options including inhaled nitrous oxide (N2O, also known as "laughing gas"), other inhaled anesthetic gases, opioids, paracervical or pudendal block, transcutaneous electrical nerve stimulation, hydrotherapy, sterile water injections, and psychoprophylaxis (Likis et al., 2012).

Inhaled nitrous oxide is a non-invasive form of pain relief. Commonly used in dentistry, nitrous oxide provides a diminished sense of pain and provides some antianxiety effects (Likis et al., 2012). In comparison to epidural anesthesia, women using nitrous oxide for pain management retain their full mobility. Individuals experience the maximum effect of nitrous oxide 30 to 60 seconds after inhalation. The effects of nitrous oxide wear off quickly and other types of pain management methods can be used in a relatively short time period after the use of nitrous oxide (Likis et al., 2012).

In the Portland-Metro region, an epidural adds an additional $1,050 to $2,400 to the cost of a hospital birth (Providence Health Services, 2015). The use of nitrous oxide costs significantly less with estimates ranging from $15 to $100 per patient.

Indications

Inhaled nitrous oxide can be used in the first or second stages of labor and is indicated for pregnant women in labor intending a vaginal birth. Nitrous oxide can also be used in the third stage of labor to assist with managing pain that may occur during immediate postpartum procedures (e.g., perineal repair, manual placenta removal).

Technology description

Inhaled nitrous oxide is widely used for childbirth pain relief outside of the United States and is a common form of non-invasive pain relief during childbirth (Klomp, van Poppel, Jones, Lazet, Di Nisio & Lagro-Janssen, 2012). Nitrous oxide is a non-flammable, tasteless, odorless gas that is self-administered on demand by laboring women through a mouth piece or facemask (Collins, Starr, Bishop, Baysiner, 2012; Klomp et al., 2012). Inhaled nitrous oxide is typically administered as a 50% nitrous oxide / 50% oxygen combination. It can be administered at this concentration using a blender device (e.g., Nitronox®) or as a premixed gas (e.g., Entonox®). Entonox® is not currently available in the U.S., but appropriate types of blender equipment are available for hospital and out-of-hospital use.

Key questions

The following key questions (KQ) guided the evidence search and review described below. For additional details about the review scope and methods please see Appendix C.

KQ1: What are the effects on mode of birth, use of neuraxial (e.g. epidural) analgesia and maternal satisfaction when nitrous oxide is used for labor analgesia?

KQ2: What are the maternal and fetal/neonatal harms of nitrous oxide used for labor pain?

Evidence review

Two systematic reviews (SR) (Klomp et al., 2012; Likis et al., 2012) identified in the core source search address the use of nitrous oxide for pain management during labor. Both SRs were of good methodological quality. The AHRQ SR (Likis, 2012; Likis, 2014) was selected as the index SR and is the primary evidence source for this coverage guidance because it is more comprehensive and matches the scope of the HERC's key questions better. In addition, the Cochrane SR (Klomp, 2012) did not add eligible studies or other information which were not included in the AHRQ SR. For further details on the methods of this evidence review please see Appendix B. The included study characteristics for the AHRQ SR are outlined below in Table 1.

Table 1. Overview of Index Systematic Review

Citation	Total Studies Included	Included Studies Specifically Addressing Coverage Guidance Scope
Likis et al (2012, 2014) [AHRQ SR]	59 studies (13 RCTs, 7 crossover RCTs, 4 non-randomized clinical trials, 14 prospective cohorts, 1 retrospective cohorts, 3 case series, 4 case-control studies, 11 cross sectional studies, and 2 trend studies)	• 14 studies (5 RCTs; 8 prospective cohorts 1 case-series) for fetal/neonatal harms • 3 studies (2 prospective cohort studies, 1 cross-sectional study) for mode of delivery • 10 studies (7 RCTs; 2 prospective cohorts; 1 cross-sectional study) for maternal adverse effects • 2 studies (both cross-sectional studies) for use of neuraxial (e.g. epidural) anesthesia

Evidence from additional sources

No additional evidence sources were included in this review. A MEDLINE® (Ovid) search based on the search strategy of the AHRQ SR did not locate any additional eligible studies.

EVIDENCE SUMMARY

The AHRQ SR (Likis, 2012) included a total of 59 studies reported in 58 publications (13 RCTs, 7 crossover RCTs, 4 non-randomized clinical trials, 14 prospective cohorts, 1 retrospective cohorts, 3 case series, 4 case-control studies, 11 cross sectional studies, and 2 trend studies) to answer five key questions on the following issues: 1) effectiveness for pain (21 studies); 2) comparative effectiveness for women's satisfaction with their birth experience and pain management (9 studies); 3) effect on mode of birth (6 studies); 4) maternal and fetal/neonatal adverse effects (49 studies); and 5) health system factors influencing the use of nitrous oxide (no studies). Key Questions 2, 3 and 4 are directly applicable to this coverage guidance.

Most of the studies in the full AHRQ SR included comparator interventions that are not of interest for this guidance (comparators included other inhaled anesthetic gasses, most of which are not used in the U.S., alternative concentrations of N2O; parenteral opioids and non-pharmacologic techniques not widely available or used in the U.S.). Many of the studies used different concentrations of N2O compared to the 50% N2O/50% oxygen mix that is used in most labor and delivery settings in countries such as the United Kingdom (U.K.) and which is the concentration used in U.S. settings that have adopted it for obstetric use. Most included studies did not report on populations or outcomes of interest for this guidance (e.g. pain scores, occupationally exposed workers). Some populations of interest (e.g. women in the third stage of labor requiring procedural analgesia such as for manual placental removal) were not explicitly included among the studies identified in the AHRQ SR. No study directly addressed or was designed to address whether availability or use of N2O reduces the use of neuraxial (e.g. epidural) analgesia; we were only able to address this outcome descriptively. None of the included studies that did address the questions of interest for this evidence review were conducted in the U.S., although all were conducted in developed countries with modern maternity care systems. However, differences in health systems, provider training, hospital routines and patient expectations may limit the applicability of these studies to the U.S. context.

Although pain was not selected as a key outcome for this guidance, for background context, the AHRQ SR found that N2O is less effective than epidural anesthesia for measures of pain in labor, but that the evidence was insufficient to determine the effectiveness compared with other, non-epidural pain management interventions. The studies are limited because of poor quality, use of varying outcome measures, and inconsistency. The review found no studies that met inclusion criteria and studied the systems factors related to using N2O for management of labor pain, including provider preferences, availability, settings and resource utilization.

Critical Outcome: Fetal/neonatal adverse effects

The AHRQ SR (Likis, 2012) noted that while 49 studies reported on maternal, fetal, neonatal, or occupational harms associated with N2O use in labor, that 16 of these were conducted prior to 1980 when it was usual practice to combine N2O with other sedative, tranquilizing and anesthetic agents. Although N2O is transmitted via the placenta to the fetus, it is also quickly eliminated via maternal circulation and neonatal respiration. Twenty-nine studies included fetal or neonatal harms as outcomes.

The SR found no significant differences between any comparison groups in Apgar scores at either one or five minutes after birth. Eight studies reported umbilical cord blood gasses. There was one study that compared infants of women using 50% N2O/50% oxygen to epidural anesthesia. It found that 7% of the N2O group had Apgar scores less than or equal to seven at one minute after birth compared to 6% of infants of women who used epidurals. At five minutes, the proportions with low Apgar scores were 1% and 4%, respectively (p values not reported). There was a statistically significant finding in one study of lower arterial cord blood gasses among infants of primiparous women who used N2O plus meperidine (a parenteral opioid) compared to those who used an epidural (pH 7.21 vs. pH 7.29, $p<0.01$). Use of meperidine alone has been associated with lower umbilical cord gasses and so it is not clear whether this finding can be attributed to N2O use or only to use of meperidine. The AHRQ SR was unable to analyze neonatal intensive care unit admission because of the varying definitions of intensive care across countries and lack of reporting of this outcome.

Only one study included in the AHRQ SR compared neonatal neurobehavioral outcomes among infants of women using N2O and who used other methods of labor pain management, including epidurals, opioids, TENS, and non-pharmacologic methods. This study reported no significant differences between groups in neonatal adaptive capacity scores (NACS).

Critical Outcome: Mode of birth

Six studies in the AHRQ review compared the mode of birth among women who used N2O to women who used other methods of pain relief and determined that there was insufficient evidence, primarily due to poor quality studies and inconsistent results. However, only three studies compared the intervention and comparator of interest for this guidance. One prospective cohort study from Ireland, published in 1987, enrolled primiparous women in an academic hospital. Twenty women used N2O and 50 women used epidural anesthesia. Other comparison groups in the study used TENS or parenteral opioids. Another prospective cohort study from Finland, published in 1994, included 210 women (27% primiparas) using N2O and 82 women (71% primiparas) using epidural anesthesia. This study also found higher rates of vaginal birth among women using N2O. No analysis of the results by parity was provided in the AHRQ SR. These two studies found the following proportions of women with vaginal, assisted vaginal (vacuum or forceps), Cesarean, or vaginal breech births as described in Table 2 below. No statistical testing of differences between pain management groups were reported in either study.

Table 2. Mode of Birth According to Pain Management Approach

Mode of Birth	Nitrous Oxide*	Epidural*
Vaginal	60%/95%	26%/80%
Assisted	35%/2%	62%/11%
Cesarean	0%/3%	6%/9%
Breech	5%/NR	6%/NR

NR: not reported

* The first percentage in each cell represents the Irish study and the second percentage is from the Finnish study.

One cross sectional study conducted in the U.K. and published in 1982 also reported the mode of birth. This U.K.-based study included women (51.4% primiparous) who had vaginal births and found that women who used N2O (n=128) were more likely to have a spontaneous vaginal birth and less likely to have an assisted vaginal birth compared with women who used epidural anesthesia (n=423) or women who used an epidural and N2O together (n=38). Proportions who had a vaginal birth for each of these three groups were 93.7%, 48.7%, and 60.5% and for assisted vaginal birth the proportions were 6.3%, 51.3%, and 39.5%.

Consistent with reported mode of birth outcomes, three of these studies (two prospective cohort studies and one cross sectional study) also reported shorter duration of labor for women in the N2O groups compared to the epidural groups. The reported duration of labor in the N2O groups ranged from a mean of 5.2 hours +/- 1.7 (standard deviation [S.D.]) to 6.7 +/- 3.0 hours. The reported range among women using epidural anesthesia was 7.7 +/- 2.4 hour to 10.8 +/- 4.9 hours.

Important Outcome: Maternal adverse effects

Most harms reported by studies included in the AHRQ SR were unpleasant side effects of N2O such as nausea, vomiting, dizziness and drowsiness. Some commonly reported adverse effect outcomes (e.g. nausea and oxygen desaturation) are reported often among women in labor regardless of pain management strategies used. Studies did not have adequate power to detect rare outcomes. Eight studies of women receiving N2O as the sole pain management agent report rates of nausea from 0% to 28%. Four of these studies also reported vomiting with a range of 0% to 14%. Four studies of women using N2O as the sole analgesia agent reported dizziness or lightheadedness, with rates ranging from 3% to 23%. Four studies reported drowsiness or sleepiness with sole use of N2O and proportions ranged from 0% to 67%.

Important Outcome: Maternal satisfaction

Nine studies in the AHRQ SR evaluated women's satisfaction with their birth experience or pain management, although most were of poor quality and reported varying outcome measures, making it difficult to synthesize results. However, the AHRQ authors concluded that there was low strength of evidence to support the equivalence or superiority of N2O relative to maternal satisfaction outcomes. Among the three studies that specifically evaluated use of 50% N2O / 50% oxygen compared with epidural anesthesia, two studies (two prospective cohorts) evaluated women's satisfaction with labor pain management at various points in time between one hour and three days post-delivery. They both reported that women who used N2O were somewhat less satisfied with the adequacy of pain relief for N2O compared to epidural anesthesia. Satisfaction scores ranged from 60% to 90% for the N2O group and 98% to 100% for the epidural group in the prospective cohort study. Because N2O is not assumed or designed to achieve the same degree of pain relief as epidural anesthesia this is not considered by the AHRQ researchers to be as robust of an outcomes as is women's assessment of whether they would use the method again. One prospective cohort study conducted in Ireland found that 80% of women who used N2O would request the method again in a subsequent pregnancy compared with 88% of women

who used an epidural. In a cross-sectional study performed in Sweden that evaluated this outcome, 69.9% of women who used N2O would request it in another pregnancy compared to 45.3% of women who used an epidural.

Important Outcome: Use of neuraxial analgesia in labor

The AHRQ SR did not report on this outcome. However, the two cross sectional studies (one from the U.K. and one from Sweden) that reported outcomes for groups of women choosing N2O and epidural anesthesia, respectively, do give some information on the methods that women choose when both choices are freely available. The U.K. based study, published in 1982, included only women who had a vaginal birth and approximately half were primiparous. Of 1000 women, about 13% used N2O, 42% used epidurals, and 4% used both methods. Other methods used in this study included parenteral opioids, pudendal or regional anesthetic blocks, no pharmacologic pain management, and combinations of these methods. The Swedish cross-sectional study, published in 1996, gathered data on women who had used N2O, epidural, local anesthesia, acupuncture, hydrotherapy, and breathing techniques as their primary pain management technique. About 79% of women used N2O and 34% used epidural (categories were not mutually exclusive and thus some women who started with N2O may have also used epidurals or other techniques).

Other Decision Factors

Resource Allocation

The cost of N2O for labor is low ($15 to $100 per patient). The major cost is for the delivery equipment, which is borne by the facility or provider. The costs of the comparator intervention are relatively high ($1,050 to $2,400 per patient per epidural in the Portland metropolitan area). Use of N2O is associated with lower rates of assisted vaginal birth and cesarean delivery which would potentially result in significantly lower intrapartum costs. For some women who use both N2O and an epidural during the same labor, anesthesia costs of care could increase over use of an epidural alone. However, this combination may still result in higher vaginal birth rates and thus lower total costs of care. The literature review found that the length of labor was consistently shorter (about 2 to 4 hours shorter) among women using N2O analgesia compared to women using epidural anesthesia such that increased use of N2O may also result in somewhat shorter length of stay on labor and delivery units.

Values and preferences

Some women and clinicians have a strong preference to avoid or delay neuraxial anesthesia and would potentially desire an intervention that may decrease their risk of assisted vaginal delivery or cesarean section. If N2O were available in Oregon facilities, many women would likely try it. Most women would not be concerned about potential harms because there do not appear to be adverse fetal/neonatal harms and women who experience adverse effects themselves can stop using N2O and their symptoms would resolve. Its quick onset would also be desired by women who are waiting for an epidural in labor and who would use it as a bridging technology. However, other women may strongly prefer neuraxial

anesthesia (epidural) because of its greater effect in reducing labor pain, so the net assessment is that values and preferences would be highly variable.

Other considerations

There is currently no specific CPT code for N2O use in labor except for an anesthesia-specific code. Benefit plans may need to consider alternative payment methodologies and/or innovative mechanisms to encourage use by providers. Facilities and clinicians may have to invest in equipment and staff training to implement N2O for labor pain. Facilities may experience shorter length of stay on labor and delivery units with increased use of N2O that may result in higher bed availability and/or decreased staffing needs in some hospitals.

POLICY LANDSCAPE

Quality measures

No quality measures related to the use of nitrous oxide during labor were identified when searching the National Quality Measures Clearinghouse.

Payer coverage policies

No public or private payer coverage policies[1] were identified for the use of nitrous oxide during labor.

Professional society guidelines

The National Institute for Health and Care Excellence (NICE) found there to be moderate evidence of benefit for the use of nitrous oxide during labor (NICE, 2014). The guideline notes that nitrous oxide can cause nausea and light-headedness for the mother. NICE did not find any evidence of harm to the baby. The use of 50:50 mixture oxygen and nitrous oxide is recommended to be available in all birth settings in the United Kingdom.

The American College of Nurse-Midwives (ACNM) has a Position Statement that supports the increased availability and use of nitrous oxide analgesia (ACNM, 2011).

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Evidence Sources

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[1] Washington Medicaid, Aetna, Cigna, Regence Blue Cross Blue Shield, and Moda

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

APPENDIX A. GRADE INFORMED FRAMEWORK - ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issue about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Confidence in the quality of the evidence, across studies, about an outcome

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

***Low*:** The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

***Very low*:** The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

APPENDIX B. GRADE EVIDENCE PROFILE

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Fetal/Neonatal Adverse Effects (Apgar scores, Cord gasses)[1]							
14	5 RCTs; 8 Prospective cohorts; 1 Case-series	High	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○
Mode of Birth[3]							
3	2 Prospective cohort; 1 Cross-sectional	High	Consistent	Direct	Imprecise	Moderate magnitude of effect and some evidence of dose-response relationship	Low confidence in estimate of effect ●●○○
Maternal Adverse Effects (Nausea, Vomiting, Dizziness/Lightheadedness, Drowsiness/Sleepiness)[2]							
10	7 RCTs; 2 Prospective cohorts; 1 Cross-sectional	High	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○
Maternal Satisfaction[3]							
4	2 Prospective cohort; 2 Cross-sectional	High	Consistent	Direct	Imprecise	None	Low confidence in estimate of effect ●●○○

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Use of Neuraxial Anesthesia[3]							
2	2 Cross-sectional	High	Consistent	Indirect	Imprecise	None	Very low confidence in estimate of effect (●○○○)

[1] Studies from Tables 9, 10, 11 (AHRQ, 2012). Strength of evidence assessment based on AHRQ SR, Table 12 (AHRQ, 2012).

[2]Studies from Table 8 (AHRQ, 2012). Strength of evidence assessment based on AHRQ SR, Table 12 (AHRQ, 2012).

[3]Studies for benefit outcomes selected from AHRQ SR based on HERC review PICO only (neuraxial anesthesia comparator studies only) (AHRQ, 2012). Strength of evidence based on risk of bias assessments included for individual studies in AHRQ SR, Table 6 (AHRQ, 2012) and assessment of other GRADE elements by staff.

APPENDIX C. METHODS

Scope Statement

Populations

Pregnant women intending a vaginal birth in the first and second stages of labor and their fetus/neonate, women in the third stage of labor or immediate postpartum period

Population scoping notes: *Exclude women planning a Cesarean birth*

Interventions

Self-administered nitrous oxide used for labor analgesia or third stage/immediate postpartum management

Intervention exclusions: *Concentration of nitrous oxide blended with oxygen for analgesia other than 50%; non-self-administration of nitrous oxide*

Comparators

Neuraxial analgesia (e.g. epidural, combined spinal/epidural)

Outcomes

Critical: Mode of birth; Fetal/neonatal adverse effects (e.g. low Apgar score, low cord blood gasses)

Important**:** Maternal adverse effects (e.g. nausea/vomiting, dizziness, loss of consciousness); Use of neuraxial (e.g. epidural) analgesia; Maternal satisfaction

Considered but not selected for the GRADE table: Use of non-neuraxial analgesia

Key Questions

KQ1: What are the effects on mode of birth, use of neuraxial (e.g. epidural) analgesia and maternal satisfaction when nitrous oxide is used for labor analgesia?

KQ2: What are the maternal and fetal/neonatal harms of nitrous oxide used for labor pain?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “nitrous oxide,” and “labor pain management.” Searches of core sources were limited to citations published after 2004.

The core sources searched included:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Health Technology Assessment (HTA) program
BMJ Clinical Evidence
Canadian Agency for Drugs and Technologies in Health (CADTH)

Cochrane Library (Wiley Interscience)
Hayes, Inc.
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

Based on this initial search, the AHRQ report (Likis, 2012) was selected as the index systematic review.

We also identified another good quality SR from the Cochrane Collaboration in the core source search. The Cochrane SR (Klomp, 2012) included four RCTs that were not included in the AHRQ SR. They were excluded from the AHRQ SR because they were not published in English. In total, five RCTs in the Cochrane SR, compared varying or unspecified concentrations of N2O to oxygen alone or no treatment. Only one of these RCTs evaluated the comparison, relevant to this coverage guidance, of 50% N2O/50% oxygen with epidural anesthesia. This RCT also included a no treatment control group. The Cochrane SR did not present outcomes for the comparison of N2O vs. epidural groups, but only the comparison of the N2O and no treatment groups. We were unable to incorporate the results of the N2O vs. epidural comparison to this evidence report due to this RCT being published in Chinese.

A MEDLINE® (Ovid) search was then conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of the AHRQ report (Likis, 2012). The search was limited to publications in English published after 2010 (the end search date for the AHRQ SR).

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Centers for Disease Control and Prevention (CDC) – Community Preventive Services
Choosing Wisely
Institute for Clinical Systems Improvement (ICSI)
National Guidelines Clearinghouse
New Zealand Guidelines Group
NICE
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, or clinical practice guidelines.

APPENDIX D. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
760.0-760.5,760.61-760.9,761.0-761.9,762.0-762.9,763.0-763.7,763.81-763.9,764.00-764.99,765.20-765.29,779.32,779.81-779.82,779.84,779.89,V30.00-V30.2,V31.00-V31.2,V32.00-V32.2,V33.00-V33.2,V34.00-V34.2,V35.00-V35.2,V36.00-V36.2,V37.00-V37.2,V39.00-V39.2	Birth of Infant
ICD-10 Diagnosis Codes	
P00.0-P00.7,P00.81-P00.9,P01.0-P01.9,P02.0-P02.1,P02.20-P02.9,P03.0-P03.6,P03.810-P03.9,P04.0-P04.3,P04.41-P04.9,P05.00,P05.10,P05.9,P29.0,P29.11-P29.2,P29.4,P29.81-P29.9,P36.0,P36.10-P36.9,P78.89,P92.01-P92.09,P94.1-P94.9,P96.0,P96.3-P96.5,P96.82-P96.89,Q27.0, Z38.00-Z38.8	Birth of Infant
CPT Codes	
01960	Anesthesia for vaginal delivery only
01961	Anesthesia for cesarean delivery only
01967	Neuraxial labor analgesia/anesthesia for planned vaginal delivery
01968	Anesthesia for cesarean delivery following neuraxial labor analgesia/anesthesia
01969	Anesthesia for cesarean hysterectomy following neuraxial labor analgesia/anesthesia

Note: Inclusion on this list does not guarantee coverage

01996	Daily management of epidural, not to include the day that the catheter is placed

CG-Nitrous oxide use for labor pain management

Question: How shall the Coverage Guidance recommendation on the use of nitrous oxide for labor pain management be applied to the Prioritized List?

Question source: Nomination process

Current Prioritized List Status:
Line: 1
Condition: PREGNANCY (See Guideline Notes 2,16,22,64,65,85,92,99,147)
Treatment: MATERNITY CARE

ICD-10: N88.3,O02.81-O02.89,O09.00-O09.13,O09.211-O09.93,O10.011-O10.93,O11.1-O11.9,O12.00-O12.23,O13.1-O13.9,O14.00-O14.93,O15.00-O15.9,O16.1-O16.9,O20.0-O20.9,O21.0-O21.9,O22.00-O22.53,O22.8x1-O22.93, O23.00-O23.43,O23.511-O23.93,O24.011-O24.93,O25.10-O25.3,O26.00-O26.53,O26.611-O26.93,O29.011-O29.93,O30.001-O30.93,O31.00x0-O31.8x99,O32.0xx0-O32.9xx9,O33.0-O33.2,O33.3xx0-O33.9,O34.00-O34.43, O34.511-O34.93,O35.0xx0-O35.9xx9,O36.0110-O36.93x9,O40.1xx0-O40.9xx9,O41.00x0-O41.93x9,O42.00, O42.011-O42.92,O43.011-O43.93,O44.00-O44.13,O45.001-O45.93,O46.001-O46.93,O47.00-O47.9,O48.0-O48.1, O60.00-O60.03,O60.10x0-O60.23x9,O61.0-O61.9,O62.0-O62.9,O63.0-O63.9,O64.0xx0-O64.9xx9,O65.0-O65.9, O66.0-O66.3,O66.40-O66.9,O67.0-O67.9,O68,O69.0xx0-O69.9xx9,O70.0-O70.9,O71.00-O71.9,O72.0-O72.3, O73.0-O73.1,O74.0-O74.9,O75.0-O75.5,O75.81-O75.9,O76,O77.0-O77.9,O80-O85,O86.11-O86.89,O87.0-O87.9, O88.011-O88.83,O89.01-O89.9,O90.1-O90.6,O90.81-O90.9,O91.011-O91.03,O91.211-O91.23,O92.011-O92.79, O98.011-O98.93,O99.011-O99.89,O9A.111 O9A.53,Q92.61,Q95.0-Q95.1,Z03.71-Z03.79,Z22.330,Z31.82,Z32.00- Z32.02,Z34.00-Z34.93,Z36,Z3A.00-Z3A.49,Z39.0-Z39.2

CPT: 01958-01963,01967-01969,12021,37191-37193,57022,59000-59100,59160-59622,59866,59871,64505-64530, 76801-76828,76945,76946,81420,81507 81512,84163,84704,88235,88267,88269,96150-96154,97802-97814, 98960-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99412,99429- 99449,99468-99480,99487-99498,99605-99607

HCPCS: G0108,G0109,G0270,G0271,G0396,G0397,G0406-G0408,G0425 G0427,G0463,G0466,G0467,H0045,S2401- S2403,S2405,S2411,S8055,S9140,S9141,S9208-S9214

Relevant codes:

01960 Anesthesia for vaginal delivery only

However, this code can only be used by anesthesiologists or nurse anesthetists.

HERC Staff Summary

This is an inexpensive, effective intervention. There are implementation issues: no specific code exists, and there are likely to be a variety of providers offering this service inside and outside of a hospital setting.

HERC Staff Recommendations:

1) Advise HSD to consider reimbursement options for the use of nitrous oxide.
2) Add a guideline

   GUIDELINE NOTE XXX NITROUS OXIDE FOR LABOR PAIN

   Line 1

   Nitrous oxide for labor pain is included on this line.

EbGS Coverage Guidance Summary

Oregon Health Evidence Review Commission

January 14, 2016

Oregon Health Authority

Oregon Health & Science University

Center For Evidence-based Policy

For HERC review and approval:

Nitrous Oxide Use For Labor Pain Management

Nitrous Oxide for Labor Pain
Primary evidence sources

Likis F. E., Andrews, J. A., Collins, M. R., Lewis, R. M., Seroogy, J. J., Starr S. A., … McPheeters, M. L. (2012). Nitrous oxide for the management of labor pain. Comparative Effectiveness Review No. 67. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 12-EHC071-EF. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://www.effectivehealthcare.ahrq.gov/ehc/products/260/1175/CER67_NitrousOxideLaborPain_FinalReport_20120817.pdf

Nitrous Oxide for Labor Pain
Clinical Background

- In the U.S., pain relief during childbirth is most commonly delivered through epidural anesthesia.
- 61% of women who had singleton vaginal births elected epidural anesthesia.
- Other pain control options include opioids, hydrotherapy, sterile water injections, psychoprophylaxis, and labor support as well as inhaled nitrous oxide.
- Inhaled nitrous oxide is widely used for childbirth pain relief outside of the United States.

Nitrous Oxide for Labor Pain
Clinical Background

- Nitrous oxide is a non-flammable, tasteless, odorless gas (N2O).
- For childbirth-related pain, N2O is typically administered as 50% nitrous oxide： 50% oxygen mixture.
- Nitrous oxide reduces the sensation of pain and provides some antianxiety effects.
- In comparison to epidural anesthesia, women using N2O retain full mobility.
- Nitrous oxide is rapidly cleared from the maternal system with normal respiration.

Nitrous Oxide for Labor Pain
Clinical Background

- Because the effects of N2O wear off quickly, other pain management methods can be used soon after N2O.
- Nitrous oxide can be used in the first or second stages of labor and is indicated for women intending a vaginal birth.
- Nitrous oxide can also be used in the third stage of labor for immediate postpartum procedures (e.g., perineal repair, manual placenta removal).
- Costs in the Portland-Metro region:
    - Epidural: $1,050-$2,400
    - Nitrous oxide: $15-$100

Nitrous Oxide for Labor Pain Evidence Summary

Outcomes	**Estimate of Effect for Outcome/** ***Confidence in Estimate***
Fetal/neonatal adverse effects *(Critical outcome)*	No significant differences in Apgar scores at 1 and 5 minutes, or umbilical cord gasses after birth when maternal N2O is compared to epidural anesthesia use. ●●●○ *(Moderate certainty, based on multiple RCTs and other studies with consistent findings)*
Mode of birth *(Critical outcome)*	Compared to women using epidural anesthesia, for those using N2O: 15 to 34 more women per 100 are likely to have an unassisted vaginal birth; 9 to 27 fewer women per 100 would experience assisted vaginal (forceps/vacuum) birth; and there would be about 6 fewer Cesarean births per 100 compared to those using epidural anesthesia for labor pain. ●●○○ *(Low certainty based on prospective cohort and cross sectional studies with consistent findings)*

Nitrous Oxide for Labor Pain Evidence Summary

Outcomes	**Estimate of Effect for Outcome/** ***Confidence in Estimate***
Maternal adverse effects *(Important outcome)*	Women may experience unpleasant side effects when using N2O. (These data come from studies of women using N2O as the sole form of labor analgesia and are not compared to any other methods.) Nausea (0-28%), vomiting (0-14%), dizziness/lightheadedness (3-23%), and drowsiness/sleepiness (0-67%) were commonly reported side effects. Effects dissipated quickly when N2O use is stopped. ●●●◌ (*Moderate certainty based on multiple RCTs and other studies with consistent findings*)

Nitrous Oxide for Labor Pain Evidence Summary

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*
Maternal satisfaction *(Important outcome)*	70 to 80% of women who used N2O said they would want to use it in a subsequent pregnancy compared to 45 to 88% of women who would request an epidural again. (These data come from studies where multiple labor pain management modalities are readily available and women using N2O or epidural were asked if they would want to use that method for a future birth.) ●●○○ (*Low certainty based on prospective cohort and cross-sectional studies with consistent findings*)
Use of neuraxial (e.g., epidural) anesthesia *(Important outcome)*	When multiple pain management methods are available for women 13% to 79% will use N2O, compared to 34 to 42% who will select epidural anesthesia. There is no direct evidence on whether availability or use of N2O changes the use of neuraxial anesthesia. ●○○○ (*Very low certainty based on cross-sectional studies with consistent findings*)

Nitrous Oxide for Labor Pain Summary

- Nitrous oxide is often used in dentistry and can be used by most pregnant women for pain in labor, as an alternative to or in addition to other pain-relieving measures.
- There do not appear to be any ill effects for infants.
- Women can experience unpleasant side effects such as nausea, vomiting, and lightheadedness.
- Most women who use nitrous oxide find it helpful and would want it again in another birth.
- The benefits of nitrous oxide seem to outweigh any harms.
- There is little recent published data about its use in U.S. settings, but an increasing number of new use locations.

HERC Coverage Guidance – Nitrous Oxide for Labor Pain
Disposition of Public Comments

Commenters

Identification	Stakeholder
A	Member of the public *[Submitted September 21, 2015]*

Public Comments

ID/#	Comment	Disposition
A1	Coverage guidance should state that nitrous oxide is a medical gas and should be handled by staff who are state licensed and acting within their scope of practice when purchasing, setting up equipment, testing equipment, handling the mask, monitoring the equipment during use, and gas scavenging. Coverage guidance should state that nitrous oxide is a medical gas and must be handled, monitored, and used in compliance with regulations and guidelines from: • Compressed Gas Association (CGA) • Occupational Safety and Health Administration (OSHA) • The National Fire Protection Association (NFPA) • The Joint Commission for the Accreditation of Healthcare Organizations (JCAHO) • Medical malpractice insurance carriers • Code of Federal Regulations (CFR) Title 41 - Public Contracts and Property Management	Thank you for your comment. Our coverage guidances make recommendations about coverage, and assume that equipment will be used by qualified and appropriately licensed personnel in accordance with all applicable regulations.

Section 7.0

Coverage Guidances-HTAS

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: PROTON BEAM THERAPY

DRAFT for VbBS/HERC meeting materials 1/14/2016

HERC Coverage Guidance

Proton beam therapy (PBT) is recommended for coverage for malignant ocular tumors (*strong recommendation*).

Proton beam therapy is recommended for coverage *(weak recommendation)* for:

- malignant brain, spinal, skull base, paranasal sinus, and juxtaspinal tumors
- pediatric malignant tumors (incident cancer under age 21)

Proton beam therapy is not recommended for coverage for cancer of the bone, breast, oropharynx, nasopharynx, esophagus, liver, lung, or prostate or for gynecologic or gastrointestinal cancers, lymphoma, sarcoma, thymoma, seminoma, arteriovenous malformation or ocular hemangiomas *(weak recommendation).*

Note: Definitions for strength of recommendation are provided in Appendix A *GRADE Informed Framework Element Description.*

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Trusted sources

Washington State Health Care Authority Health Technology Assessment Program. (2014). Proton Beam Therapy. Olympia, WA: Health Technology Assessment Program. Retrieved January 22, 2015 from http://www.hca.wa.gov/hta/Pages/proton.aspx.

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

EVIDENCE OVERVIEW

Clinical background

Protons are positively-charged subatomic particles that have been in clinical use as a form of external beam radiotherapy for over 60 years. Compared to the photon X-ray energy used in conventional radiotherapy, proton beams have physical attributes that are potentially appealing. Specifically, protons deposit radiation energy at or around the target, at the end of the range of beam penetration, a phenomenon known as the Bragg peak. The goal of any external beam radiotherapy is to deliver sufficient radiation to the target tumor while mitigating the effects on adjacent normal tissue. This has been a challenge for conventional photon therapy due to the amount of radiation deposited both before and after the target is reached. While the amount of photon radiation at entry into the body is much higher than at exit, photon beams typically "scatter" to normal tissues after leaving the target. This so-called "exit" dose is absent for protons, as tissue beyond the point of peak energy deposition receives little to no radiation**.**

Initial use of proton beam therapy (PBT) focused on conditions where sparing very sensitive adjacent normal tissues was felt to be of utmost importance, such as cancers or noncancerous malformations of the brain stem, eye, or spinal cord. In addition, proton beam therapy was advocated for many pediatric tumors because even lower-dose irradiation of normal tissue in pediatric patients can result in pronounced acute and long-term toxicity. There are also long-standing concerns regarding radiation's potential to cause secondary malignancy later in life, particularly in those receiving radiation at younger ages. Finally, radiation may produce more nuanced effects in children, such as neurocognitive impairment in pediatric patients treated with radiotherapy for brain cancers.

More recently, however, the use of PBT has been expanded in many settings to treat more common cancers such as those of the prostate, breast, liver, and lung. With the growth in potential patient numbers and reimbursement, the construction of proton centers has grown substantially. There are now 14 operating proton centers in the U.S., including one in Seattle, WA that came online in March 2013. Eleven additional centers are under construction or in the planning stages, and many more are proposed. The construction of cyclotrons at the heart of proton beam facilities is very expensive ($150-$200 million for a multiple gantry facility).

Indications

This appraisal focuses on the use of proton beam therapy (PBT) to treat patients with multiple types of cancer as well as those with selected noncancerous conditions. Within each condition type, two general populations were specified as of interest for this evaluation**:**

- Patients receiving PBT as primary treatment for their condition (i.e., curative intent)
- Patients receiving PBT for recurrent disease or for failure of initial therapy (i.e., salvage)

All forms of PBT were considered for this evaluation, including monotherapy, use of PBT as a "boost" mechanism to conventional radiation therapy, and combination therapy with other modalities such as chemotherapy and surgery. All PBT studies that met entry criteria for this review were included, regardless of manufacturer, treatment protocol, location, or other such concerns.

Conditions included in the evidence review are as follows:

- Cancers
- Bone tumors
- Brain, spinal, and paraspinal tumors
- Breast cancer
- Esophageal cancer
- Gastrointestinal cancers
- Gynecologic cancers
- Head and neck cancers (including skull base tumors)
- Liver cancer
- Lung cancer
- Lymphomas
- Ocular tumors
- Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
- Prostate cancer
- Soft tissue sarcomas
- Seminoma
- Thymoma
- Noncancerous Conditions
- Arteriovenous malformations
- Hemangiomas
- Other benign tumors (e.g., acoustic neuromas, pituitary adenomas)

Evidence review

A summary of the net health benefit of PBT vs. alternative treatments and the strength of available evidence on net health benefit, as well as an evaluation of consistency of these findings with clinical guideline statements and public/private coverage policy, can be found in Table 1. The level of comparative evidence was extremely limited for certain conditions and entirely absent for others. We identified a total of six RCTs and 37 nonrandomized comparative studies across all 19 condition types. Importantly, five of the six RCTs involved different treatment protocols for PBT and had no other comparison groups; while these are included for completeness, primary attention was paid to studies (RCTs and otherwise) that compared PBT to an alternative form of treatment.

Most of the comparative studies identified also had major quality concerns. For example, nearly all non-randomized comparative studies were retrospective in nature, and many involved comparisons of a PBT cohort to a non-contemporaneous group receiving alternative therapy. Major differences in patient demographics and baseline clinical characteristics as well as duration of follow-up were often noted

between groups. Of the 6 RCTs identified, 1, 4, and 1 were judged to be of good, fair, and poor quality respectively. Corresponding figures for non-randomized comparative studies were 1, 20, and 16.

As noted on Table 1, PBT was judged to have superior net health benefit for ocular tumors, and incremental net health benefit for adult brain/spinal tumors and pediatric cancers. PBT was comparable to alternative treatment options for patients with liver, lung, and prostate cancer as well as one noncancerous condition (hemangiomas). Importantly, however, the strength of evidence was low for all of these conditions. The evidence base for all other condition types was insufficient to determine net health benefit, including two of the four most prevalent cancers in the U.S.: breast and gastrointestinal (lung and prostate are the other two).

As with information on clinical effectiveness, data on potential harms of PBT come from RCTs, comparative cohort studies, and case series, although comparative harms data are still lacking for many condition types. Across all condition types, a total of 25 studies reported comparative information on treatment-related harms; differences in the types of harms relevant to each condition, as well as variability in harms classification even within conditions, precludes any attempt to summarily present harms data across all 19 condition categories.

Observational data on secondary malignancy with PBT are generally lacking. Two studies were identified with comparative information. One was a fair-quality matched retrospective cohort study comparing 1,116 patients in a linked Medicare-SEER database who received either PBT or photon radiation for a variety of cancers and were followed for a median of 6.4 years. On an unadjusted basis, the incidence rates of any secondary malignancy and malignancies occurring in the prior radiation field were numerically lower for PBT, but not statistically-significantly so. After adjustment for age, sex, primary tumor site, duration of follow-up, and year of diagnosis, PBT was associated with a risk of secondary malignancy approximately one-half that of photon therapy (HR=0.52; 95% CI: 0.32, 0.85; p=0.009). There are challenges with these findings, however. First and foremost, the lower rate of secondary malignancy with PBT appeared to be manifested almost entirely in the first five years after radiotherapy, a time period in which a second cancer event is not typically attributed to prior radiation (Bekelman, 2013). In addition, patients were accrued over a very long time period (1973-2001), only the very end of which included highly conformal photon techniques like IMRT.

The second study was a poor-quality retrospective cohort study comparing PBT to photon radiotherapy in 86 infants who were treated for retinoblastoma and followed for a median of 7 years (PBT) or 13 years (photon radiotherapy). Therapy was received at two different US centers (PBT at MGH and photon radiotherapy at Children's Hospital Boston). Kaplan-Meier analyses were conducted to control for differential follow-up but no adjustments were made for other differences between groups. Ten-year estimates of the cumulative incidence of secondary malignancy were numerically lower for PBT, but not statistically significantly so (5% vs. 14% for photon, p=0.12). However, when malignancies were restricted to those occurring in-field or thought to be radiation-induced, a significant difference in favor of PBT was observed (0% vs. 14%, p=0.015). In addition, significant differences in favor of PBT in both cumulative incidence and radiotherapy-related malignancy were observed for the subgroup of patients with hereditary disease.

Other harms are presented in detail for each condition type in the sections that follow.

No comparative studies were identified for curative therapy of: breast, esophageal, gastrointestinal, gynecologic, and pediatric cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations.

No comparative studies were identified for salvage treatment of: brain/spinal/paraspinal, breast, esophageal, gastrointestinal, gynecologic, pediatric, and prostate cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations and hemangiomas.

No comparative studies of harms identified for: gastrointestinal and gynecologic cancers; lymphomas, sarcomas, seminomas, and thymomas; arteriovenous malformations.

Cancers

Bone Cancer

Curative

A single poor-quality retrospective comparative cohort study evaluated PBT for primary and recurrent sacral chordomas in 27 patients. Among these patients 21 were treated with surgery and combination PBT /photon therapy (mean radiation dose: 72.8 Gray Equivalents [GyE]), in comparison to six patients who received PBT/photons alone (mean dose: 70.6 GyE). For patients with primary tumors, Kaplan-Meier estimates of local control, disease-free survival and overall survival exceeded 90% among those treated by surgery and radiation (n=14). Only two of the six patients with primary tumors received radiation alone, one of whom had local failure at four years, distant metastases at five years, and died at 5.5 years.

Salvage

In the same study of 27 patients with sacral chordomas who were treated with PBT/photon radiation alone or in combination with surgery, seven radiation/surgery patients and four radiation-only patients had recurrent disease. Among patients in the radiation/surgery group, four patients died of disease 4-10 years after treatment; the remainder was alive with disease at last follow-up. In the radiation-only group, two of four patients died of disease at 4-5 years of follow-up; the other two were alive with disease at last follow-up.

Harms

In the study described above, multiple descriptive harms were reported. Patients receiving radiation alone reported numerically lower rates of abnormal bowel or bladder function as well as difficulty ambulating in comparison to those receiving combination therapy, but rates were not statistically tested. PBT patients also reported higher rates of return to work, although this was also not tested statistically. Evidence is thus inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with bone cancer.

Brain, Spinal, and Paraspinal Tumors

Curative

Two poor-quality retrospective comparative cohort studies investigated primary PBT for brain, spinal, and paraspinal tumors. One was an evaluation of PBT (mean dose: 54.6 GyE) vs. photon therapy (mean dose: 52.9 Gy) in 40 adults (mean age: 32 years; 65% male) who received surgical and radiation

treatment of medulloblastoma at a single US cancer center. PBT patients were followed for a median of 2.2 years, while photon patients were followed for a median of nearly five years. No statistical differences between radiation modalities were seen in Kaplan-Meier assessment of either overall or progression-free survival at two years. A numeric difference was seen in the rate of local or regional failure (5% for PBT vs. 14% for photon), but this was not assessed statistically.

The second study involved 32 patients treated for intramedullary gliomas with either PBT (n=10) or IMRT (n=22). While explicit comparisons were made between groups, the PBT population was primarily pediatric (mean age: 14 years), while the IMRT population was adult (mean age: 44 years). Patients in both groups were followed for a median of 24 months; dose was >50 GyE or Gy in approximately 75% of patients. While the crude mortality rate was lower in the PBT group (20% vs. 32% for IMRT, not tested), in multivariate analyses controlling for age, tumor pathology, and treatment modality, PBT was associated with significantly increased mortality risk (Hazard Ratio [HR]: 40.0, p=0.02). The rate of brain metastasis was numerically higher in the PBT group (10% vs. 5% for IMRT), but this was not statistically tested. Rates of local or regional recurrence did not differ between groups.

Harms

In the first study described above, PBT was associated with statistically-significantly lower rates of weight loss (median % of baseline: -1.2% vs. 5.8% for photon, p=0.004) as well as requirements for medical management of esophagitis (5% vs. 57% respectively, p<0.001). PBT patients also experienced less RTOG grade 2 or greater nausea and vomiting (26% vs. 71%, p=0.004).

In the second study comparing primarily 10 pediatric patients (mean age: 14 years) receiving PBT for spinal cord gliomas to 22 adults receiving IMRT for the same condition (mean age: 44 years) (Kahn, 2011), no cases of long-term toxicity or myelopathy were reported in either group. Minor side-effect rates were reported for the overall cohort only. In summary, limited, low-quality evidence suggests that PBT is associated with reductions in acute radiation-related toxicity relative to photon radiation in patients with brain and spinal tumors.

Table 1: Summary table assessing strength of evidence, direction of benefit, and consistency with relevant guideline statements and coverage policy.

Condition	Incidence (per 100,000)	Net Health Benefit vs. Comparators	Type of Net Health Benefit	Strength of Evidence	Guideline Recommendations	Coverage Policies
Cancer						
Bone	1.3	Insufficient	---	+	M	M
Brain/spinal	9.6	Incremental	B: = H: ↓	+	U	U
Breast	97.7	Insufficient	---	o	NM	NR/NC
Esophageal	7.5	Insufficient	---	o	NM	NR/NC
GI	100.6	Insufficient	---	o	NM	NR/NC
Gynecologic	38.2	Insufficient	---	o	NM	NR/NC
Head/neck	17.2	Insufficient	---	+	NM	M
Liver	12.8	Comparable	B: = H: =	+	NM	M
Lung	95.0	Comparable	B: = H: =	+	M	M
Lymphomas	32.9	Insufficient	---	o	NR/NC	NR/NC
Ocular	1.2	Superior	B: ↑ H: ↓	++	U	U
Pediatric	9.1	Incremental	B: = H: ↓	+	U	U
Prostate	99.4	Comparable	B: = H: =	+	M	M
Sarcomas	4.8	Insufficient	---	o	NM	M
Seminoma	4.0	Insufficient	---	o	NM	NM
Thymoma	0.2	Insufficient	---	o	NM	NM
Noncancerous						
AVMs	1.0	Insufficient	---	o	NM	M
Hemangiomas	2.0	Comparable	B: = H: =	+	NM	NM
Other	2.0	Insufficient	---	o	NM	M

B: Benefits; H: Harms

Strength of Evidence: Low=+; Moderate=++; High=+++; No evidence=o

Legend: U = Universally recommended or covered; M=Mixed recommendations or coverage policies; NM=Not mentioned in guidelines or coverage policies; NR/NC=Not recommended or not covered

Esophageal Cancer

Harms

Two studies were identified that examined comparative harms in patients treated with PBT for esophageal cancer. One was a relatively large, fair-quality, retrospective comparative cohort study of 444 patients (median age: 61 years; 91% male) who were treated with chemotherapy and radiation (PBT, IMRT, or 3D-CRT) followed by surgical resection. Patients were followed for up to 60 days after hospital discharge. After adjustment for patient characteristics and clinical variables, 3D-CRT was associated with a significantly greater risk of postoperative pulmonary complications vs. PBT (Odds Ratio [OR]: 9.13, 95% CI: 1.83, 45.42). No significant differences were observed between PBT and IMRT, however. No differences in the rate of gastrointestinal complications were observed for any treatment comparison.

In addition, a fair-quality comparative study was identified that examined early impact on lung inflammation and irritation in 75 patients receiving PBT, IMRT, or 3D-CRT for esophageal cancer; patients were followed for up to 75 days following radiation. Nearly all outcome and toxicity measures were reported for the entire cohort only. However, the rate of pneumonitis was found to be significantly higher among PBT patients (33% vs. 15% for IMRT/3D-CRT, p=0.04). In summary, evidence is inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with esophageal cancer, particularly in comparison to IMRT.

Head and Neck Cancers

Curative

There were two poor-quality retrospective comparative cohorts of primary PBT in head and neck cancer. One was an evaluation of 33 patients treated with either PBT alone or PBT+photon therapy to a target dose of 76 Gy for a variety of head and neck malignancies in Japan. Treatment groups differed substantially in terms of age, gender, and duration of follow-up (mean: 5.9 vs. 3.1 years). Numeric differences in favor of PBT+photon therapy were seen for local control, recurrence, and mortality, but these were not statistically tested, nor were multivariate adjustments made for differences between groups.

The other study was a very small (n=6) comparison of endoscopic resection followed by either PBT or IMRT as well as endoscopy alone in patients with malignant clival tumors. Limited description of the study suggests that PBT was used only in cases of residual disease, while it is unclear whether IMRT was also used in this manner or as an adjuvant modality. One of the IMRT patients died of causes unrelated to disease; no other deaths were reported.

Salvage

In the first study described above, four patients were identified as having recurrent disease, three of whom received PBT alone. Two of the three PBT-only patients were alive with local tumor control at last follow-up (5 and 17 years respectively); one patient had their cancer recur three months after PBT and died in month 7 of follow-up. The one PBT+photon patient died at 2.5 years of follow-up, but was described as having local tumor control.

Harms

In the first study describe above, rates of tongue ulceration, osteonecrosis, and esophageal stenosis differed somewhat between treatment groups, but were not statistically tested. Overall toxicity rates were estimated to be 22.8% at both three and five years, but were not stratified by treatment modality.

In a separate, fair-quality study comparing rates of vision loss from radiation-induced optic neuropathy in 75 patients treated with PBT or carbon-ion therapy for head and neck or skull base tumors, unadjusted rates of vision loss were similar between modalities (8% and 6% for PBT and carbon-ion respectively, not statistically tested). In multivariate analyses controlling for demographic and clinical characteristics, treatment modality had no effect on rates of vision loss (p=0.42). Another comparison of PBT and carbon-ion therapy in 59 patients with head and neck or skull base tumors was of poor quality (due to no control for differences between patient groups) and focused on the incidence of radiation-induced brain changes. The incidence of CTCAE brain injury of any grade was significantly (p=0.002) lower in the PBT group. MRI-based assessment of brain changes showed a lower rate in the PBT group (17% vs. 64% for carbon-ion), although this was not tested statistically. In summary, evidence is inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with head and neck cancer.

Liver Cancer

Curative

Two fair-quality prospective comparative cohort studies provided evidence of the clinical effectiveness of primary use of PBT in liver cancer. One was an evaluation of 35 patients with unresectable hepatocellular carcinoma (HCC) who were treated with PBT (mean dose: 76.5 GyE) either alone or in combination with chemotherapy and were followed for up to 4 years. While statistical testing was not performed, rates of local tumor control and the proportion of patients experiencing reductions in tumor volume were nearly identical between groups.

The other study was also prospective but compared PBT to another heavy-ion modality not in circulation in the U.S. (carbon ion). In this study, a fair-quality comparison of 350 patients with HCC who received PBT (53-84 GyE) or carbon-ion (53-76 GyE) therapy and were followed for a median of 2.5 years, no statistically-significant differences were observed in 5-year Kaplan-Meier estimates of local control, no biological evidence of disease, or overall survival between treated groups.

Salvage

Two studies were identified with information on recurrent disease. One was a poor-quality comparison of PBT to conventional photon radiation in eight patients with recurrent HCC after hepatectomy. Five patients were treated with PBT (68.8-84.5 GyE), and three with photons (60-70 Gy). Seven of eight patients died of liver failure or lung metastasis a median of 1.5 years after radiation; the one patient alive at the end of follow-up was a photon patient. The rate of local tumor control was 78%, and did not differ between treatment groups.

The other study was a previously-described prospective comparison of PBT to carbon-ion therapy in 350 patients with primary or recurrent HCC. No subgroup analyses were performed, but prior treatment

history for HCC was found not to have a statistically-significant impact on local tumor control (p=0.73). Prior treatment was not examined as a risk factor for overall survival, however.

Harms

Two comparative studies were identified with comparative information on radiation-related harms. In a previously-described study of eight patients with recurrent HCC after hepatectomy, there were no instances of bone marrow depression or gastrointestinal complications in either group. Serum aspartate aminotransferase (AST) levels increased in the three photon patients and 4/5 PBT patients, although this was not tested statistically.

In the other study, a previously-described comparison of PBT to carbon-ion therapy in 350 patients with primary or recurrent HCC, rates of toxicities as graded by the Common Terminology Criteria for Adverse Events (CTCAE) framework were comparable between groups, including dermatitis, GI ulcer, pneumonitis, and rib fracture. The rate of grade 3 or higher toxicities was similar between groups (3% vs. 4% for PBT and carbon-ion respectively), although this was not statistically tested.

In summary, limited, low-quality evidence suggests that PBT is associated with comparable rates of toxicity to other radiation modalities in patients with liver cancer.

Lung Cancer

Curative

Three fair-quality comparative cohort studies examined the clinical effectiveness of PBT in lung cancer. Two studies retrospectively compared outcomes with PBT to those with IMRT or older three-dimensional conformal radiotherapy (3D-CRT) at a US cancer center. One study involved 250 patients with non-small-cell lung cancer (NSCLC) who were treated with 66 Gy of photons or 74 GyE of protons and followed for up to one year to assess a key measure of lung function known as diffusing capacity of lung for carbon monoxide (DLCO). While this measure did not differ between PBT and IMRT at 5-8 months after treatment, DLCO declined significantly more in the 3D-CRT group as compared to PBT after adjustment for pretreatment characteristics and other lung function measures (p=0.009).

A second study focused on survival in 202 patients with locally-advanced, unresectable NSCLC who were followed for a median of 1.5 years and treated 74 GyE of PBT or 63 Gy of either IMRT or 3D-CRT. Actuarial estimates of median overall survival were 24.4, 17.6, and 17.7 months for PBT, IMRT, and 3D-CRT respectively, although these differences were not statistically significant (p=0.1061).

A third study was a prospectively-measured cohort but, as with the study of liver cancer mentioned above, compared PBT to carbon ion therapy, evaluating 111 Japanese NSCLC patients over a median of 3.5 years. No statistically-significant differences between groups were observed in three-year actuarial estimates of local control, progression-free survival, or overall survival.

Salvage

In the second study described above, 22% of the study sample was identified as having a prior malignancy of any type. The effects of prior malignancy on overall survival were not reported, however.

Harms

A total of three comparative studies assessed harms in patients with lung cancer. One was a study of severe radiation-induced esophagitis (within six months of treatment) among 652 patients treated for NSCLC with PBT, IMRT, or 3D-CRT at a US cancer center. Rates of grade 3 or higher esophagitis were 6%, 8%, and 28% for PBT, 3D-CRT, and IMRT respectively ($p<.05$ for PBT and 3D-CRT vs. IMRT).

In the previously-described noncontemporaneous case series comparison of patients with locally-advanced, unresectable NSCLC who were treated with PBT, IMRT, or 3D-CRT, hematologic toxicity rates did not differ by radiation modality. Significant differences in favor of PBT were seen in rates of grade 3 or higher esophagitis (5%, 39%, and 18% for PBT, IMRT, and 3D-CRT respectively, $p<0.001$) as well as pneumonitis (2%, 6%, and 30%, $p<0.001$), while rates of grade 3 or higher dermatitis were significantly greater in the PBT group (24% vs. 17% and 7% for IMRT and 3D-CRT, $p<0.001$).

Finally, in a previously-described comparison of PBT to carbon-ion therapy in 111 patients in Japan, rates of pneumonitis, dermatitis, and rib fracture did not differ statistically between radiation modalities across all toxicity grades. In summary, moderate evidence suggests that rates of treatment-related toxicities with PBT are comparable to those seen with other radiation modalities in patients with lung cancer.

Ocular Tumors

Curative

In comparison to other cancer types, the evidence base for ocular tumors was relatively substantial. A total of seven comparative studies were identified of the clinical benefits of primary PBT in such cancers—a single RCT, four retrospective cohort studies, a comparison of a recent case series to the treatment groups from the RCT, and a comparison of noncontemporaneous case series. The RCT compared PBT alone to a combination of PBT and transpupillary thermotherapy (TTT) in 151 patients treated for uveal melanoma and followed for a median of 3 years. Combination therapy was associated with a statistically-significantly ($p=0.02$) reduced likelihood of secondary enucleation; no other outcomes differed significantly between groups. In a separate, poor-quality comparison of these findings to a separate series of patients undergoing PBT with endoresection of the scar, rates of secondary enucleation did not differ between groups, but rates of neovascular glaucoma were significantly lower in the PBT+endoresection group vs. the groups from the RCT (7% vs. 58% and 49% for PBT alone and PBT+TTT respectively, $p<0.0001$). Of note, however, median follow-up was less than two years in the PBT+endoresection series vs. 9 years in the RCT.

Three of the cohort studies were all fair-quality and involved comparisons to surgical enucleation in patients with uveal melanoma at single centers. PBT was associated with statistically-significant improvements in overall survival rates relative to enucleation at 2-5 years in two of these studies. Rates of metastasis-related and all cancer-related death were statistically-significantly lower among PBT patients through two years of follow-up in one study (n=1,051), but were nonsignificant at later timepoints. The 5-year metastasis-free survival rate in a second study (n=67) was 50% higher among PBT patients in a Cox regression model controlling for baseline characteristics (59.0% vs. 39.4% for enucleation, $p=0.02$). In the third study, Kaplan-Meier curves for all-cause mortality, melanoma-related mortality and metastasis-free survival did not statistically differ for 132 patients treated with PBT and

enucleation. Metastasis-free survival also did not differ in Cox regression adjusting for age, sex, and tumor thickness.

Another fair-quality study assessed the impact of PBT + chemotherapy vs. PBT alone in 88 patients with uveal melanoma who were followed for 5-8 years. Five-year overall survival rates did not statistically differ between groups on either an unadjusted or Cox regression-adjusted basis.

Finally, a poor-quality comparison of noncontemporaneous case series evaluated treatment with PBT + laser photocoagulation or PBT alone in 56 patients with choroidal melanoma. At one year, there were no differences in visual acuity between groups.

Salvage

A single comparative study examined PBT in recurrent ocular cancer. In this fair-quality, comparative cohort study, a total of 73 patients with uveal melanoma had recurrence of disease following an initial course of PBT at a US hospital. Patients (mean age: 58 years) were treated with either a second course of PBT (70 GyE) in five fractions or surgical enucleation and followed for 5-7 years. The likelihood of overall survival at five years was significantly (p=0.04) longer in the PBT group (63% vs. 36% for enucleation), as was the probability of being free of metastasis at this timepoint (66% vs. 31% respectively, p=0.028). Findings were similar after Cox proportional hazards regression adjusting for tumor volume and year of retreatment as well as patient age. The likelihood of local tumor recurrence at five years was 31% in the PBT group. No local recurrences were found in the enucleation group, which is not surprising given the nature of the treatment.

Harms

Two comparative studies assessed the harms of PBT for ocular cancers. In the previously-described RCT comparing PBT with thermotherapy to PBT alone in 151 patients with uveal melanoma, no statistically-significant differences were observed between groups in rates of cataracts, maculopathy, papillopathy, glaucoma, or intraocular pressure. The combination therapy group had a significantly lower rate of secondary enucleation (p=0.02), although actual figures were not reported.

In a previously-described comparison of PBT to enucleation in 132 patients treated for unilateral choroidal tumors, rates of eye loss in the PBT arm were assessed and estimated to be 26% at five years of follow-up. In summary, limited, low-quality evidence suggests comparable rates of harm for PBT relative to treatment alternatives in patients with ocular tumors.

Pediatric Cancers

Harms

PBT's theoretical potential to lower radiation-induced toxicity in children serves as the comparative evidence base. Comparative studies are lacking, most likely due to a lack of clinical equipoise.

Other than the study of secondary malignancy described above, no comparative studies of the potential harms of PBT in patients with pediatric cancers were identified.

Prostate Cancer

Curative

The largest evidence base available was for prostate cancer (10 studies). However, only 6 of these studies reported clinical outcomes *and* compared PBT to alternative treatments. These included an RCT, a prospective comparative cohort, and four comparisons of noncontemporaneous case series.

The included RCT was a fair-quality comparison of 202 patients with advanced (stages T3-T4) prostate cancer who were randomized to receive either photon therapy with a proton boost (total dose: 75.2 GyE) or photons alone (67.2 Gy) and were followed for a median of five years. Kaplan-Meier estimates of local tumor control, disease-specific survival, and overall survival were similar at both 5- and 8-year timepoints among the entire intent-to-treat population as well as those completing the trial (n=189). However, in patients with poorly-differentiated tumors (Gleason grades 4 or 5), local control at 8 years was significantly better in patients receiving PBT+photons (85% vs. 40% for photons alone, p=0.0014).

The prospective cohort study was a fair-quality comparison of patient-reported health-related QoL at multiple timepoints among 185 men (mean age: 69 years) with localized prostate cancer who were treated with PBT, PBT+photons, photons alone, surgery, or watchful waiting. Overall QoL, general health status, and treatment-related symptom scales were employed. No differences in overall QoL or general health status were observed at 18 months of follow-up, although men treated with PBT monotherapy reported better physical function in comparison to surgery (p=0.01) or photon radiation (p=0.02), and better emotional functioning in relation to photon radiation (p<0.001). Men receiving PBT+photons also reported significantly fewer urinary symptoms at 18 months in comparison to watchful waiting (p<0.01).

Outcomes were also assessed in three comparisons of noncontemporaneous case series. One was a fair-quality evaluation of high-dose PBT+photons (79.2 GyE) in 141 patients enrolled in a clinical trial who were matched on clinical and demographic criteria to 141 patients treated with brachytherapy. Patients were followed for a median of eight years. Eight-year actuarial estimates of overall survival, freedom from metastasis, and biochemical failure did not statistically differ between groups. The proportion of patients achieving a nadir PSA level of ≤0.5 ng/mL as of their final measurement was significantly higher in the brachytherapy group (92% vs. 74% for PBT, p=0.0003).

Two additional studies were deemed to be of poor quality due to a lack of control for confounding between study populations. One was a comparison of a cohort of 206 brachytherapy patients compared with the same PBT+photon group described above. The difference in the percentage of patients achieving nadir PSA after a median of 5.4 years of follow-up was similar to that reported in the study above (91% vs. 59%), although statistical results were not reported. Five-year estimates of disease-free survival (using biochemical failure definitions) did not statistically differ between groups. The other study involved comparisons of bowel- and urinary-related QoL in three distinct cohorts receiving PBT (n=95; 74-82 GyE), IMRT (n=153; 76-79 Gy), or 3D-CRT (n=123; 66-79 Gy). Statistical changes were assessed within (but not between) each cohort immediately following treatment as well as at 12 and 24 months of follow-up, and were also assessed for whether the change was considered “clinically meaningful” (>0.5 SD of baseline values). Some differences in QoL decrements were seen at earlier timepoints. However, at 24 months, all groups experienced statistically and clinically significant decrements in bowel QoL, and none of the groups had significant declines in urinary QoL.

A fourth, poor-quality comparison of case series involved an evaluation of patient-reported outcomes on the Expanded Prostate Cancer Index Composite (EPIC) questionnaire among a cohort of 1,243 patients receiving PBT for prostate cancer and a group of 204 patients receiving IMRT from a previous multicenter study. Statistically-significant differences between treatment groups were observed for many baseline characteristics, only some of which were adjusted for in multivariate analyses. No differences were observed in summary scores for bowel, urinary, and sexual QoL at two years, although more IMRT patients reported specific bowel frequency (10% vs. 4% for PBT, p=0.05) and urgency (15% vs. 7%, p=0.02) problems at two years.

Harms

Four comparative studies examined the harms associated with PBT and alternative treatments in patients with prostate cancer. The previously-described RCT of PBT+photon therapy vs. photons alone examined rates of rectal bleeding, urethral stricture, hematuria, incontinence, and loss of full potency; no patients in either arm had grade 3 or higher toxicity during radiation therapy. Actuarial estimates of rectal bleeding at eight years were significantly higher in the PBT+photon arm (32% vs. 12% for photons alone, p=0.002), although this was primarily grade 2 or lower toxicity. Rates of urethral stricture, hematuria, incontinence, and loss of potency did not differ between groups.

Three additional studies involved retrospective comparisons using available databases. The most recent was a matched comparison of 314 PBT and 628 IMRT patients treated for early-stage prostate cancer using the linked Chronic Condition Warehouse-Medicare database with a focus on complications occurring within 12 months of treatment. At six months, rates of genitourinary toxicity were significantly lower in the PBT arm (5.9% vs. 9.5%, p=0.03). This difference was not apparent after 12 months of follow-up, however (18.8% vs. 17.5%, p=0.66). Rates of gastrointestinal and other (e.g., infection, nerve damage) complications did not statistically differ at either timepoint.

Another recent study compared matched cohorts of men with prostate cancer in the linked Medicare-SEER database who were treated with PBT or IMRT (684 patients in each arm) and followed for a median of four years. IMRT patients had a statistically-significantly lower rate of gastrointestinal morbidity (12.2 vs. 17.8 per 100 person-years, p<0.05). No other statistical differences were noted in genitourinary morbidity, erectile dysfunction, hip fracture, or use of additional cancer therapy.

Finally, there was an analysis of nearly 30,000 men in the Medicare-SEER database who were treated with PBT, IMRT, 3D-CRT, brachytherapy, or conservative management (observation alone) and evaluated for gastrointestinal toxicity. All forms of radiation had higher rates of GI morbidity than conservative management. In pairwise comparisons using Cox proportional hazards regression, PBT was associated with higher rates of GI morbidity than conservative management (HR: 13.7; 95% CI: 9.1, 20.8), 3D-CRT (HR: 2.1; 95% CI: 1.5, 3.1), and IMRT (HR: 3.3; 95% CI: 2.1, 5.2).

In summary, moderate evidence suggests that rates of major harms are comparable between PBT and photon radiation treatments, particularly IMRT.

Noncancerous Conditions

Ocular Hemangiomas

Curative

A single poor-quality retrospective study evaluated PBT's clinical effectiveness in 44 patients with diffuse or circumscribed choroidal hemangiomas who were treated with either PBT (20-23 GyE) or photon therapy (16-20 Gy) and followed for an average of 2.5 years. Unadjusted outcomes were reported for the entire cohort only; reduction in tumor thickness, resolution of retinal detachment, and stabilization of visual acuity were observed in >90% of the overall sample. In Kaplan-Meier analysis of outcomes adjusting for differential follow-up between treatment groups, therapeutic modality had no statistically-significant effects on stabilization of visual acuity (p=0.43).

Harms

A single, previously-described retrospective comparative cohort study assessed outcomes in patients with circumscribed or diffuse hemangiomas treated with PBT or photon radiation. Small differences in unadjusted rates of optic nerve/disc atrophy, lacrimation (formation of tears) and ocular pressure as well as effects on the retina, lens, and iris were observed between groups, but most side effects were grade 1 or 2. The rate of retinopathy was substantially higher in PBT patients (40% vs. 16% for photons). However, in Cox proportional hazards regression adjusting for between-group differences, no effect of radiation modality on outcomes was observed, including retinopathy (p=0.12).

Other Benign Tumors

Curative

Two comparative studies of PBT's clinical effectiveness in other benign tumors were both of poor quality. One was a retrospective cohort of consisting of 20 patients with giant-cell bone tumors who were treated with PBT+photon therapy (mean: 59 GyE) or photons alone (mean: 52 Gy) and followed for median of 9 years. Patients could also have received partial tumor resection. Of note, the PBT population consisted entirely of young adults (mean age: 23 years), while the photon-only population was much older (mean: 46 years); no attempt was made to control for differences between treatment groups. Rates of disease progression, progression-free survival, and distant metastases were numerically similar between groups, although these rates were not statistically tested.

The other study was a small cohort study comparing PBT alone, photon therapy alone, or PBT + photons in 25 patients with optic nerve sheath meningioma. On an overall basis, visual acuity improved in most patients. Rates did not numerically differ between treatment groups, although these were not tested statistically.

Salvage

In the first study described above, five of 20 were identified as having recurrent disease. Two of the five were treated with PBT+photon therapy, one of whom had progression of disease at eight months but no further progression after retreatment at five years of follow-up. The other patient was free of local progression and metastases as of 9 years of follow-up. In the three photon patients, one had local progression at 12 months but no further progression as of year 19 of follow-up, one patient was free of progression and metastases as of five years of follow-up, and one patient had unknown status.

Harms

The previously-described study comparing PBT, PBT+photon, and photon therapy alone in 25 patients treated for optic nerve sheath meningiomas showed numerically lower rates of acute orbital pain and headache for both PBT groups compared to photon therapy, and numerically higher rates of late asymptomatic retinopathy. None of these comparisons were tested statistically, however. Evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities in patients with other benign tumors.

Cost & Cost-Effectiveness

Limited data are available about costs of PBT in most types of cancer. One study of breast cancer patients in the US examined reimbursement for treatment with 3D-conformal partial breast irradiation using protons or photons vs. traditional whole breast irradiation. Payments included those of treatment planning and delivery as well as patient time and transport. Total per-patient costs were substantially higher for PBT vs. photon partial irradiation ($13,200 vs. $5,300) but only modestly increased relative to traditional whole breast irradiation ($10,600), as the latter incurred higher professional service fees and involved a greater amount of patient time. Two additional studies from the same group assessed the cost-effectiveness of PBT vs. photon radiation among women with left-sided breast cancer in Sweden. In the first of these, photon radiation was assumed to increase the risk of ischemic and other cardiovascular disease as well as pneumonitis relative to PBT; clinical effectiveness was assumed to be identical. Reductions in adverse events led to a gain in quality-adjusted life years (QALYs) equivalent to approximately one month (12.35 vs. 12.25 for photon). Costs of PBT were nearly triple those of photon therapy, however ($11,124 vs. $4,950), leading to an incremental cost-effectiveness ratio (ICER) of $65,875 per QALY gained. The other study used essentially the same model but focused attention only on women at high risk of cardiac disease (43% higher than general population). In this instance, a much lower ICER was observed ($33,913 per QALY gained).

One study evaluated the economic impact of PBT in lung cancers among patients in the Netherlands. A Markov model compared PBT to carbon-ion therapy, stereotactic radiation therapy, and conventional radiation in patients with stage 1 non-small-cell lung cancer (NSCLC) over a 5-year time horizon. Effects of therapy included both overall and disease-related mortality as well as adverse events such as pneumonitis and esophagitis. For inoperable NSCLC, PBT was found to be both more expensive and less effective than either carbon-ion or stereotactic radiation and was therefore not included in subsequent analyses focusing on inoperable disease. While not reported in the paper, PBT's derived cost-effectiveness relative to conventional radiation (based on approximately $5,000 in additional costs and 0.35 additional QALYs) was approximately $18,800 per QALY gained.

Three decision analyses were available that focused on pediatric cancers, all of which focused on a lifetime time horizon in children with medulloblastoma who were treated at 5 years of age. In a US-based model that incorporated costs and patient preference (utility) values of treatment and management of adverse events such as growth hormone deficiency, cardiovascular disease, hypothyroidism, and secondary malignancy, PBT was found to generate lower lifetime costs ($80,000 vs. $112,000 per patient for conventional radiation) and a greater number of QALYs (17.37 vs. 13.91). Reduced risks for PBT were estimated based on data from dosimetric and modeling studies. Sensitivity

analyses on the risk of certain adverse events changed the magnitude of PBT's cost-effectiveness, but it remained less costly and more effective in all scenarios.

Pediatric medulloblastoma was assessed in two modeling studies. As with the analysis above, PBT was assumed to reduce both mortality and nonfatal adverse events relative to conventional photon therapy. On a per-patient basis, PBT was assumed to reduce lifetime costs by approximately $24,000 per patient and increase quality-adjusted life expectancy by nearly nine months (12.8 vs. 12.1 QALYs). On a population basis, 25 medulloblastoma patients treated by PBT would have lifetime costs reduced by $600,000 and generate an additional 17.1 QALYs relative to conventional photon radiation.

Finally, four studies were identified that examined costs and cost-effectiveness of PBT for prostate cancer. An analysis of the 2008-2009 Chronic Condition Warehouse examined treatment costs for matched Medicare beneficiaries with prostate cancer who received PBT or IMRT. Median Medicare reimbursements were $32,428 and $18,575 for PBT and IMRT respectively (not statistically tested).

A relatively recent Markov decision analysis estimated the lifetime costs and effectiveness of PBT, IMRT, and stereotactic body radiation therapy (SBRT) for localized prostate cancer. Clinical effectiveness and impact on mortality were assumed to be equivalent across all three groups. SBRT was found to have the lowest treatment costs and shortest time in treatment of the three modalities, and produced slightly more QALYs (8.11 vs. 8.05 and 8.06 for IMRT and PBT respectively) based on an expected rate of sexual dysfunction approximately half that of IMRT or PBT. SBRT was cost-saving or cost-effective vs. PBT in 94% of probabilistic simulations.

An earlier decision analysis estimated the potential cost-effectiveness of a hypothetically-escalated PBT dose (91.8 GyE) vs. 81 Gy delivered with IMRT over a 15-year time horizon. The model focused on mortality and disease progression alone (i.e., toxicities were assumed to be similar between groups), and assumed a 10% reduction in disease progression from PBT's higher dose. This translated into QALY increases of 0.42 and 0.46 years in 70- and 60-year-old men with intermediate-risk disease respectively. Costs of PBT were $25,000-$27,000 higher in these men. ICERs for PBT vs. IMRT were $63,578 and $55,726 per QALY for 70- and 60-year-old men respectively.

Finally, the model also evaluated costs and outcomes for a hypothetical cohort of 300 65 year-old men with prostate cancer. PBT was assumed to result in a 20% reduction in cancer recurrence relative to conventional radiation as well as lower rates of urinary and gastrointestinal toxicities. PBT was estimated to be approximately $8,000 more expensive than conventional radiation over a lifetime but result in a QALY gain of nearly 4 months (0.297). The resulting cost-effectiveness ratio was $26,481 per QALY gained.

EVIDENCE SUMMARY

Proton beam therapy (PBT) has been used for clinical purposes for over 50 years and has been delivered to tens of thousands of patients with a variety of cancers and noncancerous conditions. Despite this, evidence of PBT's comparative clinical effectiveness and comparative value is lacking for nearly all conditions under study in this review. As mentioned previously, it is unlikely that significant comparative study will be forthcoming for childhood cancers despite uncertainty over long-term outcomes, as the

potential benefits of PBT over alternative forms of radiation appear to be generally accepted in the clinical and payer communities. In addition, patient recruitment for potential studies may be untenable in very rare conditions (e.g., thymoma, arteriovenous malformations). In other areas, however, including common cancers such as breast and prostate, the poor evidence base and residual uncertainty around the effects of PBT is highly problematic.

The net health benefit of PBT relative to alternative treatments is rated “Superior” (moderate-large net health benefit) in ocular tumors and “Incremental” (small net health benefit) in adult brain/spinal and pediatric cancers. The net health benefit is judged “Comparable” (equivalent net health benefit) in several other cancers, including liver, lung, and prostate cancer, as well as ocular hemangiomas. It should be noted, however, that judgments of comparability were made based on a limited evidence base that provides relatively low certainty that PBT is roughly equivalent to alternative therapies. While further study may reduce uncertainty and clarify differences between treatments, it is currently the case that PBT is far more expensive than its major alternatives, and evidence of its short or long-term relative cost-effectiveness is lacking for many of these conditions. It should also be noted that evidence was examined for 11 cancers and noncancerous conditions not listed above, and it was determined that there was insufficient evidence to obtain even a basic understanding of PBT’s comparative clinical effectiveness and comparative value.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for ocular tumors (excluding hemangiomas)	Superior benefit, fewer harms	Moderate	Moderate; expensive, but lowered projected costs due to greater benefit and fewer harms	Low variability (preference for PBT)	Recommended for coverage (*strong recommendation)*	Moderate quality evidence demonstrates PBT is superior to other therapies with fewer harms, although at a greater cost, and many patients would choose this.
PBT for adult malignant brain/spinal tumors	Comparable benefit but fewer harms.	Very Low**	Moderate; expensive, but lowered projected costs due to fewer harms	Low variability (preference for PBT)	Recommended for coverage (*weak recommendation*)	There is very low quality evidence of incremental benefit compared to alternatives, but also with higher costs. People would likely choose what is thought to have fewer harms and greater benefit.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for skull base, paranasal sinus, and juxtaspinal tumors	Comparable benefit but fewer harms.	Very Low**	Moderate, expensive, but lowered projected costs due to fewer harms	Low (preference for PBT)	Recommended for coverage *(weak recommendation)*	The subcommittee heard expert testimony that skull-base tumors were one of the first uses of proton beam therapy in the 1960s and that reduction in harms to surrounding structures while delivering adequate dosimetry to tumor tissue is the primary consideration in treatment planning. Based on comparable benefit and fewer harms, allowing for higher costs but patient preference, weak recommendation for coverage.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for malignant pediatric tumors	Comparable benefit but fewer harms.	Very Low**	Moderate, expensive, but lowered projected costs due to fewer harms	Moderate (significant concerns regarding radiation therapy, given variety of tumors may have options for alternative therapies)	Recommended for coverage *(weak recommendation)*	Very low quality evidence suggests comparable benefit, and fewer harms, with a potential health impact over decades. There is a strong theoretical benefit for reducing secondary tumors although there is not good evidence to support this. Cost-effectiveness analyses suggest long term cost savings with PBT for pediatric tumors. There is a lack of clinical equipoise and therefore future studies on this are unlikely.
PBT for liver cancer	Comparable benefit, comparable harms	Low	High	Moderate	Do not recommend (*weak recommendation*)	There is low quality evidence that PBT has comparable benefits and harms to alternatives, but is more expensive,
PBT for lung cancer	Comparable benefit, comparable harms	Low	High	Moderate	Do not recommend (*weak recommendation*)	Low quality evidence of similar effectiveness, similar risk, and more cost.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for prostate cancer	Comparable benefit, comparable harms	Low	High	Moderate	Do not recommend (*weak recommendation*)	There is low quality evidence of similar effectiveness, similar risk, and more cost. There may be improved local control in poorly differentiated prostate cancer (Glisan 4-5) but no demonstrated impact on survival.
PBT for ocular hemangiomas	Comparable benefit, comparable harms	Very Low	High	Moderate to high, due to uncertainty of benefit	Do not recommend *(weak recommendation)*	Very low quality evidence exists, but it is suggesting comparable benefit. Given that there are alternatives available with similar risk and less expensive, recommendation against coverage.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PBT for bone, breast, oropharyngeal, nasopharyngeal, esophageal, GI, gynecologic, lymphomas, sarcomas, seminomas, thymomas, AVMs, and other noncancerous conditions	Unknown	Bone: Low All others: No evidence	High	Moderate (many would not choose PBT due to cost, need to travel, uncertain benefit)	Do not recommend (weak recommendation)	, Unknown benefit and unknown risk compared to alternative, and increased cost.

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee, except as specified.

** The Quality of Evidence rating was assigned by the HERC Subcommittee.

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Quality measures

No quality measures were identified when searching the National Quality Measures Clearinghouse.

Professional society guidelines

Guidelines on the use of proton beam therapy are available from the National Comprehensive Cancer Network (NCCN, 2013-2014), American Society for Radiation Oncology (ASTRO, 2013), American College of Radiology (ACR, 2011-2013), American Cancer Society (ACS), and the Alberta Health Services in Canada (2013).

Bone Cancer

NCCN guidelines state that for unresectable high- and low-grade chondrosarcomas of the skull base and axial skeleton, PBT may be indicated to allow for high-dose treatment. Alberta guidelines recommend PBT for sarcomas, including chordoma and chondrosarcoma. According to the ACR, PBT-based treatment plans are considered inappropriate (rated 1-2) in spinal and non-spinal bone metastases.

Brain, Spinal, and Paraspinal Tumors

Alberta guidelines recommend PBT as an option for CNS lesions including craniopharyngioma, germ cell tumors and low-grade gliomas.

Head and Neck Cancers

For ethmoid and maxillary sinus tumors, NCCN considers PBT an investigative therapeutic technique only. Alberta guidelines state that treatment with PBT for adults with acoustic neuromas, and paranasal sinus and nasal cavity tumors is recommended.

Lung Cancer

NCCN considers PBT appropriate for non-small-cell lung cancer. ACR recommends against use of PBT for NSCLC patients with poor performance status or requirements for palliative treatment, while Alberta guidelines do not recommend PBT for NSCLC.

Lymphomas

NCCN states that PBT may be appropriate for patients with Hodgkin and Non-Hodgkin lymphoma as well as soft tissue sarcomas; however, long-term studies are necessary to confirm benefits and harms. Alberta guidelines do recommend PBT for lymphomas only in patients less than 30 years of age.

Ocular Tumors

NCCN guidelines for treatment options in ocular tumors are under development. Alberta guidelines recommend PBT for ocular melanoma.

Pediatric Tumors

Guidelines from Alberta recommend consideration of PBT for pediatric tumors including ependymomas, rhabdomyosarcoma, Ewing's sarcoma, pineal tumors, and patients requiring craniospinal irradiation.

Prostate Cancer

NCCN and Alberta guidelines do not recommend PBT for use in prostate cancer, as superior or equivalent effects have not been demonstrated in comparison to conventional external-beam therapy. In a position statement, ASTRO concluded that the evidence supporting the use of PBT in prostate cancer continues to develop and define its role among current alternate treatment modalities. ASTRO strongly supports the provision of coverage with evidence development to evaluate the comparative effectiveness of PBT relative to other options including IMRT and brachytherapy. The ACR Appropriateness Criteria® consider PBT for treatment planning in T1 and T2 prostate cancer to be appropriate but with lower ratings than for IMRT (6-7 versus 8-9, based on a 1-9 scale).

Non-cancerous conditions

Alberta Health Services guidelines recommend PBT for benign conditions such as AVMs and meningiomas.

APPENDIX A. GRADE INFORMED FRAMEWORK – ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[1]

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

***Low*:** The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

[1] Includes risk of bias, precision, directness, consistency and publication bias

***Very low*:** The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

APPENDIX B. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
170.0-170.9	Malignant neoplasm of bone and articular cartilage
171.0-171.9	Malignant neoplasm of connective and other soft tissue
189.0	Malignant neoplasm of kidney, except pelvis
190.0	Malignant neoplasm eyeball, except conjunctive, cornea, retina, choroids
190.5	Malignant neoplasm of retina
190.6	Malignant neoplasm of eye, choroid
191.0-191.9	Malignant neoplasm of brain
192.1-192.3	Malignant neoplasm of cerebral meninges, spinal cord, spinal meninges
194.0	Malignant neoplasm of adrenal gland
194.3	Malignant neoplasm of pituitary gland and craniopharyngeal duct
194.4	Malignant neoplasm of pineal gland
198.3	Secondary malignant neoplasm, brain and spinal cord
209.29	Malignant carcinoid tumors of other sites
225.0-225.9	Benign neoplasm of brain and other parts of nervous system
227.3	Benign neoplasm of pituitary gland
234.8	Carcinoma in situ of other specified sites (pituitary)
237.0	Neoplasm of uncertain behavior of pituitary gland
239.7	Neoplasm of unspecified nature, endocrine gland (pituitary)
437.3	Cerebral aneurysm, non-ruptured
437.8-437.9	Other and unspecified cerebrovascular disease
747.81	Anomalies of the cerebrovascular system (AVM)
185	Malignant neoplasm of prostate
198.82	Secondary malignant neoplasm, genital organs
233.4	Carcinoma in situ, prostate
ICD-10 Diagnosis Codes	
C40.00-C41.9	Malignant neoplasm of bone and articular cartilage
C47.0-C47.9	Malignant neoplasm of peripheral nerves and autonomic nerves
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C64.1-C64.9	Malignant neoplasm of kidney, except renal pelvis
C69.20-C69.22	Malignant neoplasm of retina
C69.30-C69.32	Malignant neoplasm of choroid
C69.40-C69.42	Malignant neoplasm of ciliary body
C70.0-C70.9	Malignant neoplasm of meninges
C71.0-C71.9	Malignant neoplasm of brain
C72.0-C72.9	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C74.00-C74.92	Malignant neoplasm of adrenal gland
C75.1-C75.3	Malignant neoplasm of pituitary gland, craniopharyngeal duct, pineal gland
C7A.8	Other malignant neuroendocrine tumors
C79.31	Secondary malignant neoplasm of brain
C79.40-C79.49	Secondary malignant neoplasm of other and unspecified parts of nervous system
D09.3	Carcinoma in situ of thyroid and other endocrine glands [pituitary]
D32.0-D32.9	Benign neoplasm of meninges

D33.0-D33.9	Benign neoplasm of brain and other parts of central nervous system
D35.2	Benign neoplasm of pituitary gland
D44.3-D44.4	Neoplasm of uncertain behavior of pituitary gland, craniopharyngeal duct
D49.7	Neoplasm of unspecified behavior of endocrine glands and other parts of nervous system [pituitary]
I67.1	Cerebral aneurysm, nonruptured
I67.89-I67.9	Other and unspecified cerebrovascular disease
Q28.2	Arteriovenous malformation of cerebral vessels
C61	Malignant neoplasm of prostate
C79.82	Secondary malignant neoplasm of genital organs
D07.5	Carcinoma in situ of prostate
ICD-10 Procedure Codes	
D0004ZZ	Beam radiation of brain using heavy particles (protons, ions)
D0014ZZ	Beam radiation of brain stem using heavy particles (protons, ions)
D0064ZZ	Beam radiation of spinal cord using heavy particles (protons, ions)
D0074ZZ	Beam radiation of peripheral nerve using heavy particles (protons, ions)
D8004ZZ	Beam radiation of eye using heavy particles (protons, ions)
DP004ZZ-DP0C4ZZ	Beam radiation of bone using heavy particles (protons, ions) [by site; includes codes DP004ZZ, DP024ZZ, DP034ZZ, DP044ZZ, DP054ZZ, DP064ZZ, DP074ZZ, DP084ZZ, DP094ZZ, DP0B4ZZ, DP0C4ZZ]
DT004ZZ	Beam radiation of kidney using heavy particles (protons, ions)
DW014ZZ	Beam radiation of head and neck using heavy particles (protons, ions)
DW024ZZ	Beam radiation of chest using heavy particles (protons, ions)
DW034ZZ	Beam radiation of abdomen using heavy particles (protons, ions)
DW064ZZ	Beam radiation of pelvic region using heavy particles (protons, ions)
CPT Codes	
32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (proton or particle beam), entire course of treatment
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77421	Stereoscopic X-ray guidance for localized of target volume for the delivery of radiation therapy
77432	Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session)
77435	Stereotactic body radiation therapy, treatment management, per treatment course, 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex
HCPCS Level II Codes	
S8030	Scleral application of tantalum ring(s) for localization of lesions for proton beam therapy

Note: Inclusion on this list does not guarantee coverage

Proton Beam therapy Coverage Guidance and the Prioritized List

Question: How should proton beam therapy be represented on the Prioritized List?

Question source: HTAS, HERC Staff

Issue: The DRAFT Coverage Guidance on Proton Beam Therapy has been approved through HTAS. It needs to be applied to the Prioritized List.

Proton beam therapy (PBT) is recommended for coverage for malignant ocular tumors (*strong recommendation*).

Proton beam therapy is recommended for coverage *(weak recommendation)* for:

- malignant brain, spinal, skull base, paranasal sinus, and juxtaspinal tumors
- pediatric malignant tumors (incident cancer under age 21)

Proton beam therapy is not recommended for coverage for cancer of the bone, breast, oropharynx, nasopharynx, esophagus, liver, lung, or prostate or for gynecologic or gastrointestinal cancers, lymphoma, sarcoma, thymoma, seminoma, arteriovenous malformation or ocular hemangiomas *(weak recommendation).*

Current Prioritized List Status:

Code	Description	List Status
77520	Proton treatment delivery; simple, without compensation	117 CANCER OF EYE AND ORBIT 130 BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD 299 CANCER OF BRAIN AND NERVOUS SYSTEM 377 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS
77522	Proton treatment delivery; simple, with compensation	117,130,299,377
77523	Proton treatment delivery; intermediate	117,130,299,377
77525	Proton treatment delivery; complex	117,130,299,377

HERC Staff Assessment

Proton beam therapy codes are currently placed on four lines, only two of which are for malignant tumors. The other two lines (intrathoracic and brain) are for benign tumors only, which requires review. Because of the new proposed coverage of

pediatric malignant tumors, there will be multiple additional lines to which these codes would need to be added.

HERC Staff Recommendations:

1) **Add proton beam therapy codes (77520, 77522, 77523,77525) to the following lines** (based on expert recommendation):
    a. 97 CHILDHOOD LEUKEMIAS
    b. 133 GRANULOMATOSIS WITH POLYANGIITIS
        i. This is because the lethal midline granuloma code (M31.2) is on this line
    c. 195 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
    d. 205 CANCER OF BONES
    e. 242 ACUTE PROMYELOCYTIC LEUKEMIA
    f. 280 CANCER OF SKIN, EXCLUDING MALIGNANT MELANOMA
    g. 292 CANCER OF ORAL CAVITY, PHARYNX, NOSE AND LARYNX
    h. 402 ACUTE MYELOID LEUKEMIA
    i. 403 MYELOID DISORDERS

2) **Consider removal of proton beam therapy codes** from the benign lines:
    a. Line 130 BENIGN NEOPLASM OF THE BRAIN AND SPINAL CORD
        i. Experts strongly advocate for continuing to cover proton beam therapy for benign brain tumors
        ii. Staff recommendation – do not remove
    b. Line 377 BENIGN NEOPLASM OF RESPIRATORY AND INTRATHORACIC ORGANS
        i. Staff recommendation – remove from line 377. Not included for malignant tumors in this region.

3) **Add a new guideline**

    GUIDELINE NOTE XXX PROTON BEAM THERAPY FOR CANCER
    Lines 97, 133, 195, 205, 242, 280, 292, 402, 403

    Proton beam therapy is included on lines 133, 205, and 292 only for:

    - malignant brain, spinal, skull base, paranasal sinus (including lethal midline granuloma), and juxtaspinal tumors

    Proton beam therapy is additionally included on lines 97, 195, 242, 280, 402, and 403 only for:
    - pediatric malignant tumors (incident cancer under age 21)

Health Evidence Review Commission Coverage Guidance Summary

October 1, 2015

Oregon Health Authority

Oregon Health & Science University

Center For Evidence-based Policy

Coverage Guidance

For HERC review and approval

- Proton Beam Therapy

Proton Beam Therapy
Process Overview

- Evidence search (Jan 2015)
- HTAS – 2/2015, 6/2015, 9/2015
- Expert Testimony
- Extensive Public Comment (24 commenters)

Proton Beam Therapy
Clinical Background

- Protons – positively charged subatomic particles
- Proton beams – deposit radiation energy at or around target at the end of beam range
  - No exit dose radiation
- Treatment types
  - Primary treatment – curative intent
  - Recurrent disease – salvage treatment

Proton Beam Therapy
Clinical Background

Included cancerous conditions

- Bone tumors
- Brain, spinal, and paraspinal tumors
- Breast cancer
- Esophageal cancer
- Gastrointestinal cancers
- Gynecologic cancers
- Head and neck cancers (including skull base tumors)
- Liver cancer
- Lung cancer
- Lymphomas
- Ocular tumors
- Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma)
- Prostate cancer
- Soft tissue sarcoma
- Seminoma
- Thymoma

Included non-cancerous conditions

- Arteriovenous malformations
- Hemangiomas
- Other benign tumors (e.g., acoustic neuromas, pituitary adnomas

Proton Beam Therapy
Evidence Summary

- Bone cancer – low quality evidence of effectiveness, unknown risk, higher cost
- Brain, spinal, and paraspinal tumors – very low quality evidence of incremental benefit and higher costs
- Esophageal cancer – no evidence on effectiveness, unknown risk, higher cost
- Head and neck cancers – very low quality evidence of comparable benefits, fewer harms, higher costs, but patient preference

Proton Beam Therapy
Evidence Summary

- Liver cancer – low quality evidence of comparable benefits and harms, higher costs
- Lung cancer – low quality evidence of comparable benefits, similar risk, higher cost
- Ocular tumors – moderate quality evidence of greater benefits with fewer harms
- Pediatric cancers – very low quality evidence of comparable benefits, fewer harms, potential health impact over decades

Proton Beam Therapy
Evidence Summary

- Prostate cancer – low quality evidence of similar benefits, similar risk, higher cost
- Ocular hemangiomas – very low quality evidence of comparable benefits and harms
- Other benign tumors – no evidence on effectiveness, unknown risk compared to alternative, higher cost

Proton Beam Therapy
Public Comment Summary

- Comment received in support of PBT for
  - Brain, spinal, and paraspinal tumors
  - Breast cancer
  - Gastrointestinal cancers
  - Head and neck cancers (including skull base tumors)
  - Liver cancer
  - Lung cancer
  - Lymphomas
  - Pediatric cancers (e.g., medulloblastoma, reinoblastoma, Ewing's sarcoma)
  - Prostate cancer

Proton Beam Therapy
Core issues raised by expert/public

- Recurrent cancers
- Definition of pediatric
- Longevity of benefit (children, lymphomas)
- Coverage with evidence development
- Noncomparative studies
- Dosimetric modeling
- Relative costs

HERC Coverage Guidance – Proton Beam Therapy
Disposition of Public Comments

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Commenters

Identification	Stakeholder
A	Seattle Cancer Care Alliance Proton Therapy Center, Medical Director (Washington State)
B	Patient (Washington State)
C	Assistant professor, Department of Radiation Oncology, University of Washington, Seattle Cancer Care Alliance (Washington State)
D	Friend of patient
E	Friend of patient (Washington State)
F	Friend of patient (Washington State)
G	Radiation Oncologist, Corvallis, OR
H	Assistant Professor, Department of Radiation Oncology, University of Washington Medical Center (Washington State)
J	Professor and Chair, Dept. of Radiation Medicine/Professor, Division of Hematology/Oncology, Knight Cancer Institute, Oregon Health & Science University
K	Citizen (no further info provided) (Washington State)
L	Radiation Oncology, University of Washington
M	Health Policy Analyst, American Society for Radiation Oncology (ASTRO)
N	Assistant Professor, Department of Radiation Oncology, Department of Neurological Surgery, UW School of Medicine
O	Friend of patient
P	President, Particle Therapy Cooperative Group – North America
Q	Associate Professor, University of Washington Medical Center, Department of Radiation Oncology
R	Assistant Professor, University of Washington Department of Radiation Oncology
S	Associate Professor, University of Washington Department of Radiation Oncology
T	Retired nurse, Lynden, WA
U	Prostate cancer patient (WA)
V	Unknown

W	Assistant Professor, University of Washington Department of Radiation Oncology
X	Unknown
Y	Executive Director, National Association for Proton Therapy

Public Comments

ID	#	Comment	Disposition
A	1	Thank you for the opportunity to submit scientific information on Proton Beam Radiation Therapy (PBRT). PBRT eliminates the exit radiation dose that patients would otherwise receive if treated with X-rays, thereby protecting normal tissue from damaging radiation exposure. This technique allows the oncologist to (1) increase the dose delivered to tumor in order to improve local control (LC) for radiation resistant tumors and/or (2) reduce acute and long-term morbidity by minimizing normal tissue exposure. These benefits translate into not only an improvement in clinical outcomes, but quality of life and reduction of the short and long-term cost of side effect management due to functional impairment. For these reasons, we feel that it is important that Oregon residents continue to have access to this important weapon for the treatment of cancer. We welcome the opportunity to serve as an on-going resource to this Commission.	Thank you for your comments.
A	2	National Coverage Guidance Supporting the Use of Proton Beam Therapy The National Comprehensive Cancer Network (NCCN) guidelines support the use of protons for a variety of malignancies where clinical outcomes with standard therapy is suboptimal.	NCCN guidelines are summarized in the document under "Policy Landscape."
A	3	Additionally, a number of distinguished national cancer organizations have released model policy guidelines for the judicious and appropriate coverage for PBRT in patients who are most likely to benefit.	Specific guidelines are not named by the commenter. The CG document lists guidelines from the National Comprehensive Cancer Network (NCCN, 2013-2014), American Society for Radiation Oncology (ASTRO, 2013), American College of Radiology (ACR, 2011-2013), American Cancer Society (ACS), and the Alberta Health Services in Canada (2013).
A	4	We also note that the Medicare contractor for Oregon currently provides for PBRT coverage.	Thank you for the information.
A	5	The model policy from the American Society for Radiation Oncology (ASTRO), the pre-eminent and largest radiation oncology organization, released after the Washington HTA report, is one that we call your attention as strong initial	ASTRO guidelines are considered under the "Policy Landscape"

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		policy framework for coverage.	section of the CG document; a model payer policy is not appropriate for inclusion as evidence.
A	6	2014 Washington State Health Care Authority Health Technology Assessment (HTA) The 2014 Washington HTA on PBRT highlighted the need to gather additional clinical data. We agree with this; in fact, 97% of patients treated at our center are enrolled in either a clinical trial or prospective registry. While long-term efficacy and toxicity data is maturing, we routinely utilize dosimetric comparative data to determine appropriate utilization of PBT. For this reason, we feel that excluding all comparative dosimetric studies was a significant methodological flaw in the Washington HTA report. Dosimetric data is routinely utilized for clinical decision making in radiation oncology. In short, if you can deliver greater dose to the tumor or reduce normal tissue exposure, this is expected to benefit our patients. Finally, we strongly encourage you to support payer coverage with clinical evidence generation for disease sites where dosimetric comparisons suggest superiority of PBT, but clinical evidence is not yet available.	Dosimetric comparative trials of proton beam therapy would only be applicable to this coverage guidance if conventional modalities (such as IMRT) were one of the treatment arms, or if comparison to conventional radiotherapy were not feasible to obtain.
A	7	Summary of Evidence The body of clinical evidence supporting the appropriate use of protons continues to grow. Due to space considerations, we present a small sampling of the evidence. However, we remain available to present a more comprehensive view to this Commission	Thank you for presenting additional sources of evidence.
A	8	*Head & Neck Cancers* – A comparative effectiveness study from MD Anderson suggests that use of intensity modulated PBRT in advanced stage head and neck cancer was less costly and of higher value than IMRT [Frank et al, Oncology Payers 2014] (1).	Frank et al is a costing analysis comparing the experiences of two individual patients. Oncology Payers is not a peer-reviewed journal and is not identified by MEDLINE®, it does not meet the standard for inclusion.
A	9	A meta-analysis evaluating the role of photons and charged particle therapy for sinonasal carcinoma demonstrated improved disease-free survival (DFS) and LC with charged particle therapy; subgroup analysis comparing IMRT and PBRT confirmed that 5-year DFS was significantly higher at five years for patients receiving PBRT (72% versus 50%) [Patel et al, Lancet Oncol 2014] (2).	Patel 2014 was published after the WAHTA, which judged evidence to be insufficient on head & neck cancers. It is a MA of 43 cohorts. A subgroup analysis comparing proton beam

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			therapy with intensity-modulated radiation therapy showed significantly higher disease-free survival at 5 years (relative risk 1·44, 95% CI 1·01–2·05; p=0·045) and locoregional control at longest follow-up (1·26, 1·05–1·51; p=0·011). Authors encourage prospective study with patient-oriented outcomes to confirm findings. This level of evidence is generally not considered sufficient to guide coverage; however, the subcommittee discussed that RCTs may not be feasible or ethical in this setting and that reduced harms in treatment of sinonasal carcinoma with PBT would justify a recommendation for coverage.
A	10	*Breast Cancer*– A recent population-based study of 2168 woman, [Darby et al N Engl J Med. 2013] (3) found that collateral radiation exposure to the heart during breast cancer X-ray treatment increases the subsequent rate of ischemic heart disease.	Darby et al conducted a case-control study of major coronary events in patients who underwent radiotherapy for breast cancer from 1958 to 2001 in Sweden and Denmark. This was prior to modern advances in radiotherapy when radiation doses are generally lower, and does not address comparative safety of PBT.

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A	11	PBRT can significantly reduce this exposure. Macdonald et al reported the results of a prospective trial of protons after mastectomy for patients with excellent clinical outcome and significant reduction in heart dose when compared to X-rays. [Macdonald et al Int J Radiat Oncol Biol Phys. 2013] (4)	MacDonald et al is a noncomparative study of 12 individuals receiving PBT for breast cancer. While a lower heart dose theoretically will decrease future toxicity, study authors concluded "it is too early to determine cardiopulmonary toxicities in our study" as follow-up was conducted at 4 and 8 weeks.
A	12	*Prostate Cancer*– In a recent publication from the University of Florida, 5 year outcomes from 3 prospective trials of PBT for prostate cancer were reported. Five year rates of biochemical and clinical freedom from disease progression were 99%, 99%, and 76% in low, intermediate, and high risk patients, respectively. Reported toxicity rates were low. These results compare very favorably with those published for IMRT. [Mendenhall et al, Int J Radiat Oncol Biol Phys 2014] (5). We highlight our center's participation in the ongoing "PartiQOL" randomized trial comparing IMRT vs protons for prostate cancer.	The Mendenhall study is a noncomparative observational study of 211 patients; its early outcomes (2012) are included in Table 13, Appendix F (single-arm case series) of the WA HTA report.
A	13	*The True Cost of Protons*- In addition to the significant and growing body of clinical evidence, the cost-effectiveness of PBRT has also been explored. We would highlight that although PBRT is more resource-intensive to deliver upfront, it is aligned with the judicious use of health care dollars. Several recent studies, including these from Harvard have shown that when the costs of side-effects are accounted for, PBRT actually significantly *reduces* health care costs when compared to standard radiation therapy. Therefore, protons when used appropriately are *cost-effective* when compared to photon beam radiotherapy due to reduced hospitalization rates, etc. for side effect management. [Mailhot-Vega Cancer 2013 (6); Mailhot-Vega Cancer 2015 (7)].	Mailhot-Vega 2013 is included in the Washington HTA analysis. Mailhot-Vega 2015 is a Markov cohort-simulation model looking specifically at growth-hormone deficiency in pediatric cancers.
A	14	We urge the Commission to support the coverage of proton therapy and welcome the opportunity to serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians.	Thank you for your comments.
B	15	I am commenting on the proposed policy regarding Proton Therapy.	Thank you for your comments.
B	16	I was diagnosed in February 2012 with prostate cancer after having a biopsy. My PSA reading had been climbing the previous 2 years and when it reached 10.7, I had the biopsy done. The biopsy showed that I had cancer. My urologist, who was a surgeon, suggested having surgery in August of 2012. He also set me up to speak to a radiation oncologist. I had a CT & Pet scan plus explanations on the different forms of radiation treatments that were available, conventional x-	Thank you for your comments. The coverage guidance does reference one fair-quality prospective cohort study of

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		rays and seeds. Also at this time I joined a local prostate support group. I spoke with the men in the support group plus other men I had met that had prostate cancer to find out how they were doing. I spoke with the men who had surgery or either of the two forms of radiation treatments done. Many of them had procedures done years before. None had Proton Therapy or had heard of it. Every single man I spoke with, no matter how healthy they were or how well their procedure went were still having some form of issue. The two main areas of problems were incontinence and sexual function. They had different degrees of problems, from slight to serious, but all of them had something.	patient-reported quality of life among 185 men treated for prostate cancer. "No differences in overall QoL or general health status were observed at 18 months of follow-up" (p 13).
B	17	I spoke with a former vice president of my company who was treated for prostate cancer 6 years before at Loma Linda with Proton Therapy. He has had no long-term side effects. When he did his research he talk to over 100 Proton Therapy patients and came to the conclusion that because of the minimal long term side effects it was the best way to go. So I started researching on the Internet and found the same information about the lack of side effects with Proton Therapy. Also, at that time I found out that a Proton Therapy facility was being built in Seattle and would open spring of 2013. I made my decision that this was the best way to go. I went for 9 weeks of treatment; I continued to work the whole time not missing a single day. I went to work in the morning, went for treatments during midday, and then returned to work after treatment. I had no issues during treatment. By the way, I am a bicycle commuter (year round), I ride round trip 14 miles a day for work and I continued to do this even during my treatments. My wife would pick me up and take me to treatments. I am also an avid cross-country skier during the winter months.	Thank you for your comments.
B	18	My urologist had told me that if I had done surgery I would be off work for about 3 months, if I had selected x-rays or seeds I would be off work also for a period of time. Since the end of my treatments I have had 6 follow up PSA tests and my reading keeps going down. It is 0.52 now from the high of 10.7. I have had absolutely no side effects from the Proton treatment since completing treatment in June 2013. I continue to ride my bike to and from work each day. Each August I do a bike ride of 186 miles, which I do with my son each year. No problems. I don't believe I would be doing any of this or enjoying it as much if I had incontinence issues. Try biking or skiing wearing some form of diaper. Can it be done, yes. Would it be enjoyable, probably not. There has been no change in my health from before Proton treatment to now, except the lack of cancer. Is Proton Therapy the right treatment for everyone? I can't answer that, only a doctor or a person with prostate cancer can answer that. But in my case I thank God I found out about it and decided to go that route for treatment.	Thank you for your comments.
B	19	One thing I keep noticing about this whole debate about insurance companies not wanting to pay for Proton Therapy is it seems to come down to cost. Yes, proton Therapy is more expensive than the other more "accepted" forms of cancer treatment, but does anyone actually look at the long term cost from the possible long-term side effects of surgery, x-rays or seeds? I have never seen it mentioned anywhere. Quite frankly it seems no one really cares about the cost of side effects once the patient is out the door. But to me having to spend the rest of my life possibly in diapers or on some other form of medicine for side effects did not thrill me at all. By the way I am 61 years old. I plan on being around for quite a while longer.	Cost and cost-effectiveness analyses, including costs of adverse effects, are considered in the CG document.

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B	20	The last thing I want to say is, please don't take away or limit the Proton Therapy option for others who may come after me.	Thank you for your comments.
C	21	After reviewing the commission's draft on coverage guidance for proton beam therapy (PBT), I would like to highlight and summarize the pertinent, existing evidence supporting the selective use of protons as part of lymphoma treatment.	Thank you for your comments.
C	22	Lymphoma is a heterogeneous disease entity comprised of Hodgkin (HL) and non-Hodgkin lymphoma (NHL). As such, the decision on which radiation technique is best suited for a patient (e.g. PBT vs IMRT/VMAT vs 3D vs other) incorporates multiple variables including patient age, tumor location, and histology.	Thank you for your comments.
C	23	The commission is correct that currently no clinical outcomes data exists comparing photons and protons among HL or NHL patients. In HL patients, in whom the goal is to minimize morbidity and toxicity without compromising already excellent cure rates, the outcomes of interest (e.g. cardiovascular disease [CVD], second malignancy [SM]) generally require at least a decade of follow-up as no intermediate biomarker currently exists as a short-term endpoint.	Thank you for your comments. It is noted that improvements in long-term toxicities will take time to appear in trials.
C	24	Up to 75% of HL patients have disease in the thorax, and the long-term radiation-associated morbidity to this area has been clearly documented including increased rates of cardiac events (1), decreased lung function (2), breast cancer (3), lung cancer (4) and esophageal cancer (5). Furthermore, in these studies, the risk of a SM increased with increasing radiation dose to the lung, breast, or esophagus (i.e. linear no threshold), implying that the lower the radiation dose to these structures, the lower the risk of SM.	Thank you for providing these data on the risk of secondary malignancy in treatment of Hodgkins lymphoma.
C	25	Risk of toxicity appears related to the radiation dose to and volume of normal thoracic structure irradiated (2, 6) and likely will decline in the future as radiation dose and target volumes (i.e. involved-node versus involved field radiation) are currently being reduced. Nonetheless, radiation technique (PBT vs other) may still play an important role as dosimetric comparative studies using modern radiation target volumes and dose demonstrate that, on average, PBT was associated with lower dose to the heart, lungs, and breasts compared with 3D conformal and VMAT photon techniques (7). Based on risk estimates, proton technique was associated with the lowest life-years lost (7). Other dosimetric comparison studies have also shown similar, significant reduction of dose to the heart (8), breast (9, 10), lung (9, 10), and total body (9).	Commenter provides background information on risk of damage to surrounding structures with conventional radiation, and posits that PBT provides lower dose to such structures.
C	26	Thus far, the early results of involved-node radiation with protons demonstrate excellent relapse-free and event-free survival (11), suggesting that target volume coverage and local control is not compromised by using a more conformal technique. Admittedly, the ten to twenty year-local control, event-free survival, overall survival, and late toxicity after treatment with involved-node proton radiation, as compared with 3D conformal photon radiation, will be the gold standard on which to base clinical decisions and cost-effective analyses. Cost can be calculated over various time periods, but arguably for lymphoma patients, this time period should be evaluated over at least 20-30 years, which is	Commenter notes that Hodgkins patients can expect to live decades, making late toxicity an important outcome. However, late toxicity would also be a concern for other cancers that

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		when late effects of treatment may manifest and impact the patient, medical system, and society from a productivity and financial standpoint. By reducing dose to normal organ structures without compromising oncologic outcomes, protons may, in the long term, be associated with less cost secondary to fewer complication rates. Until then, I would urge you to consider the existing, preliminary data suggesting the dosimetric advantages of protons for treatment of lymphoma. Rapid adoption of reduced target volumes (e.g. involved-node radiation) among the radiation oncology community has, in part, been driven by the basic understanding that reducing dose to surrounding normal tissues will decrease acute and late morbidity for our patients.	occur in early adulthood with a high likelihood of survival. Recommendation for noncoverage was made due to lack of comparative clinical outcomes data. In cases where clinical outcomes data could be obtained, dosimetric information was felt to be inadequate to demonstrate a superior clinical outcome.
C	27	Please do not hesitate to contact me if you have any additional questions, clarifications, or concerns.	Thank you for your comments.
D	28	I support and encourage your covering proton radiation therapy for all forms of cancer or at least liver cancer where it has proven to be efficacious. I encourage you to begin covering it now, not in 3, 5, 10 years. A very close friend of our's sister needs this therapy immediately. She needs your help. She is 'covered' by Regence Blue Shield OR. After all, is that not what insurance is for. Thank you	Commenter addresses Regence; nevertheless, thank you for your comments.
E	29	Please set the example for the country. We have these therapies that give people hope to live longer, yet we make it such a fight. Not fair to family and sick person. I am not sure why drug company does not pay for some of this with regency insurance or any insurance. Please help families stop suffering and let insurance companies and drug companies work together for these treatments. Advocating for our sick health system to get better and for my friend who wants to try this treatment.	Commenter is a resident of Washington State. Thank you for your comments.
F	30	Please cover proton therapy for all forms of cancer, or at very least, liver cancer. Our close friend's sister from Medford is dying of liver cancer, has been approved for proton therapy, but pending insurance coverage decision by Oregon. Thank you for your consideration of this live saving request.	Commenter is a resident of Washington State. Thank you for your comments.
G	31	Between 1984 and 1988 I was a faculty member in the department of Radiation Oncology at Massachusetts General Hospital and Harvard Medical School. My primary clinical responsibility was proton radiation treatment at the Harvard Cyclotron Laboratory which was the first proton facility in the US. Subsequently I spent 18 years in the Department of Radiation Oncology at the University of Washington School of Medicine. Since 2006 I have been in a community practice in Corvallis. Oregon.	Thank you for your comments.
G	32	Through my years in practice I have used virtually all types of radiation treatments available for treating malignancies.	Thank you for your comments.

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		Protons have the very significant advantage of delivering the lowest integral dose to a patient; in other words, normal tissues receive less dose with protons than with any other type of radiation including intensity modulated photon radiation treatments. Randomized control studies and nonrandomized comparative studies as discussed in the HERC document show at least equivalent tumor control rates for PBT compared to photons in many tumor types with decreased toxicity in some tumor sites.	Studies mentioned by commenter are addressed in CG document.
G	33	Decreased integral dose with PBT has considerable advantages in pediatric malignancies. Growth and development are adversely impacted by radiation. PBT causes less injury. The HERC document describes several studies demonstrating the benefits of PBT in pediatric patients. Secondary malignancy reduction takes many years of followup to study. Preliminary data as cited in this document indicates a reduction in secondary malignancy.	As noted on Table 1, PBT was judged to have incremental net health benefit for pediatric cancers.
G	34	Primary brain, skull base and spinal malignancies also benefit from PBT because of decreased integral dose. The physical/spatial characteristics of PBT allow sufficient dose to be delivered to skull base and primary spinal malignancies. All parts of the brain perform important functions. PBT reduces dose to uninvolved areas of the brain in primary brain tumor treatment. This benefit in neurological function can be difficult to demonstrate using standard methods, but with sufficiently sensitive measurements improved function would mostly likely be seen.	As noted on Table 1, PBT was judged to have incremental net health benefit for adult brain/spinal tumors.
G	35	I strongly suggest that HERC reconsider their coverage recommendations to align with the Washington State HTCC recommendations.	Thank you for your comments.
H	36	Thank you for the opportunity to submit scientific information on Proton Beam Radiation Therapy (PBRT). PBRT eliminates the exit radiation dose that patients would otherwise receive if treated with X-rays, thereby protecting normal tissue from damaging radiation exposure. This technique allows the oncologist to (1) increase the dose delivered to tumor in order to improve local control (LC) for radiation resistant tumors and/or (2) reduce acute and long-term morbidity by minimizing normal tissue exposure. These benefits translate into not only an improvement in clinical outcomes, but also quality of life and reduction of the short and long-term cost associated with side effect management. For these reasons, we feel that it is important that Oregon residents continue to have access to this important weapon for cancer treatment.	See comment A1.
H	37	PBRT for non-small cell lung cancer (NSCLC) is currently recommended by the National Comprehensive Cancer Center Guidelines (NCCN V4.2014) and should not be considered experimental, investigational, or unproven.	Guidance from professional organizations on PBRT for lung cancer is mixed. NCCN does recommend; however ACR and Alberta guidelines do not. The SR finds comparable benefits and harms at increased cost; therefore the recommendation

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			is to not cover.
H	38	*Locally Advanced NSCLC*: Definitive chemoradiotherapy is the standard of care for locally advanced non-small cell lung cancer, however this treatment has the potential to carry significant toxicity. At present, LC with standard dose radiotherapy in locally advanced disease is suboptimal, with 50-60% patient experiencing relapse of their disease. One approach to improve LC is increasing the radiation dose delivered to the cancer. However, this potential improvement comes at the expense of greater toxicity. Unfortunately, attempts at dose escalation with standard X-rays in lung cancer have hit a 'toxicity ceiling' whereby the resulting increased toxicity from dose actually may reduce survival, based upon a recent randomized trial with X-rays (1).	Commenter references Bradley JD et al 2015, demonstrating that 74Gy radiotherapy had no additional benefit and possibly increased mortality compared to 60Gy radiotherapy, or a "toxicity ceiling."
H	39	In a phase II trial of dose-escalated PBRT concurrent with chemotherapy for 44 patients with stage III NSCLC, MD Anderson demonstrated reduced the side effects, which permitted safe dose escalation to 74 Gy (2). The median overall survival time was 29.4 months, compared with 19 months for patients who were treated with 74Gy with X-rays in RTOG 0617. No patient experienced grade 4 or 5 proton-related adverse events. Based upon these promising results, the RTOG has launched a phase III randomized trial of protons vs photons (RTOG 1308) for locally advanced NSCLC. Our center is participating in this trial.	Commenter notes ongoing research on PBRT in locally-advanced NSCLC given evidence of superior tumor control when 74 Gy is delivered via PBT (Chang 2011, case series of 44 patients). A Phase III trial is in progress. Three comparative studies discussed in the CG have found that "rates of treatment-related toxicities with PBT are comparable to those seen with other radiation modalities in patients with lung cancer."
H	40	*Medically Inoperable Early Stage NSCLC:* The current standard therapeutic approach for these patients is stereotactic body radiation therapy (SBRT) or hypofractionated radiotherapy with photons, which provide excellent results. However, patients with centrally located tumors are at a11-fold higher risk of high-grade toxicity or death with SBRT due to radiation exposure to the heart and mediastinal structures. (3) Therefore until a "safe dose" is established, SBRT with photons is relatively contraindicated in patients with centrally located tumors.	Commenter references Timmermann 2006, study of SBRT in 70 patients too frail to undergo surgical resection of NSCLC. Hilar/pericentral location was a strong predictor of high-grade toxicity. No comparison to PBRT is included.
H	41	Bush *et al*. reported the long-term results of a prospective trial of high-dose hypofractionated PBRT for 111 patients with medically inoperable NSCLC. OS improved with increasing dose (51, 60, and 70 Gy) with a 4-year OS of 18%, 32%,	Commenter notes that SBRT may not be used for centrally located tumors, whereas PBRT

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		and 51%, respectively (P=0.006). (4)	may improve survival by allowing delivery of higher radiation doses. The studies of PBRT in medically inoperable NSCLC were non-comparative and were included in the review by the Washington HTA. Additionally, there is an ongoing RCT (NCT00915005) comparing photon and proton therapy for locoregionally advanced NSCLC (stages II-IIIb, no specific exclusion of patients with medically inoperable tumors).
H	42	Additionally, patients with centrally located tumors did not experience excessive or increased toxicity when compared with peripherally located tumors. (4) This is in contrast to the clinical experience with X-rays. These prospective studies demonstrate that protons are safe and effective for patients with centrally located NSCLC who are medically inoperable. This has ***not*** yet been demonstrated with X-rays.	See comment H41.
H	43	*Patients with NSCLC who require re-irradiation:* Options are limited for patients previously treated with radiation and who subsequently experience intrathoracic NSCLC recurrence. These patients have a poor response to chemotherapy; surgery is extremely high-risk and usually contraindicated.	Commenter notes patients who fail initial radiation have limited options.
H	44	Due to their favorable dose-deposition characteristics, protons are uniquely suited to delivery radiation in this clinical setting. The MD Anderson group reported the results on thirty-one patients (94%) who completed reirradiation with protons. At a median 11 months' follow-up, 1-year rates of overall survival, progression-free survival, locoregional control, and distant metastasis-free survival were 47%, 28%, 54%, and 39%. Rates of severe (grade 3) toxicity were 9% esophageal, 21% pulmonary; 1 patient had grade 4 esophagitis, and 2 had grade 4 pulmonary toxicity. These data demonstrate the feasibility and efficacy of PBRT in this clinical setting. (5)	There is no comparative evidence currently available that demonstrates the superiority of PBRT to other forms of radiation therapy, surgery, chemotherapy, or palliative care for intrathoracic recurrence of NSCLC.
H	45	*The Cost of Protons for Lung Cancer*- Patients with lung cancer experience significant toxicity with standard X-ray based therapy.	Commenter references evidence of toxicity above, see H 40.
H	46	Emerging data demonstrate that protons, when used appropriately, can be *cost-effective* when compared to photon	See comment A 13.

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		beam radiotherapy due to reduced hospitalization rates, etc. for side effect management. (6,7)	
H	47	We performed a similar analysis of cost using these methods for lung cancer patients and found that for patients treated with IMRT experiencing high grade pulmonary or esophageal toxicities had costs that ***exceeded*** patients treated with protons without this toxicity.	Commenter notes internal analysis demonstrating cost savings with decreased toxicity. Reference to publication not provided.
H	48	We urge the Commission to support the coverage of proton therapy for lung cancer and welcome the opportunity to serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians. Thank you for this opportunity.	Thank you for your comments.
J	54	Thank you for the opportunity to submit scientific information on Proton Beam Radiation Therapy (PBRT). I am writing this letter to you in my capacity as Chairman of the Department of Radiation Medicine at Oregon Health Sciences University (OHSU). At the present time, OHSU does not have a proton beam facility and we do not derive any financial benefit from the delivery of proton beam radiation to patients in Oregon. However, we feel that it is important that Oregon residents have access to this important weapon for the treatment of cancer and have sent a number of our patients to proton beam facilities in other states. We send these select patients for proton radiation because we feel strongly that it is in their best clinical interest. While we do not feel that all patients benefit from protons, there are patients, especially pediatric patients in whom protons allow us to reduce risk of normal tissue injury due to radiation exposure in a manner that simply is not achievable with X-rays.	Thank you for your comments.
J	55	National Coverage Guidance Supporting the Use of Proton Beam Therapy I would like to highlight that a number of distinguished national cancer organizations have released model policy guidelines for the judicious and appropriate coverage for PBRT in patients who are most likely to benefit. I would call to your attention that the current draft of the HERC guidelines are out of step with these guidelines.	Guidelines from several organizations are included in the CG document under the "Policy Landscape" section and were considered by the HTAS.
J	56	The model policy from the American Society for Radiation Oncology (ASTRO), the pre-eminent and largest radiation oncology organization, released after the Washington HTA report, is one that we call your attention as a strong initial policy framework for coverage.	See comment A 5.
J	57	I would strongly encourage you to support payer coverage with clinical evidence generation for disease sites where dosimetric comparisons suggest superiority of PBT, but clinical evidence is not yet available. The value of this approach is highlighted in the article by Bekelman and Hahn in the Journal of Clinical Oncology (Bekelman and Hahn, JCO 2014).	Commenter suggests recommendation for coverage with evidence development. Discussion of coverage with evidence development and/or reference pricing is not in the

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			purview of this subcommittee.
J	58	Summary of Evidence The body of clinical evidence supporting the appropriate use of protons continues to grow. Due to space considerations, I am presenting a small sampling of the evidence.	Thank you for your comments.
J	59	Pediatric Tumors: In a landmark article, Oeffinger et al [N Engl J Med, 2006] showed that pediatric patients had between 5-10 times the risk of developing severe health complications after radiotherapy compared to their untreated siblings. For medulloblastomas where the radiation treatment involves the brain and spinal cord, data from MD Anderson shows that the ratio of relative risk (RRR) (proton/photon) of cardiac mortality ranged from 0.12 to 0.24. Obviously this is a substantial reduction in risk of injury and mortality in pediatric patients receiving proton beam radiotherapy [Zhang, Rad & One, 2014]	Oeffinger 2006 refers to the Childhood Cancer Survivor Study, a retrospective study of 10,397 survivors and 3034 siblings, which assessed incidence of chronic health conditions among cancer survivors compared to cancer-free siblings. Zhang 2014 is a treatment planning study of 17 pediatric medulloblastoma patients. "Passively scattered proton CSI provides superior predicted outcomes by conferring lower predicted risks of second cancer and cardiac mortality than field-in-field photon CSI for all medulloblastoma patients in a large clinically representative sample in the United States, but the magnitude of superiority depends strongly on the patients' anatomical development status." HTAS has chosen to recommend coverage of PBT for pediatric patients.
J	60	In the case of rhabdomyosarcomas of the head and neck, particularly the orbit, proton radiotherapy allows the	Childs 2012 is included in the

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		treatment of the tumor with much less dose to the brain and growing bones of the skull. Childs et al [Int J Radiat Oneal Bioi Phys, 2012] reported on 17 patients with parameningeal tumors treated at the Massachusetts General Hospital and found local control rates similar to historical treatments with photon radiotherapy but with fewer side effects. Similar considerations apply when treating neuroblastomas and Wilms tumors where standard photon treatments give higher radiation doses to the bowel and kidneys than would be delivered with protons.	WAHTA report.
J	61	Brain tumors as a class are the most common pediatric solid tumor. Merchant et al reviewed neurocognitive data for patients treated at St. Jude's, correlated this with radiation doses delivered to various areas of normal brain, calculated the doses that would have been delivered with proton radiotherapy and concluded that the reduced dose afforded by proton radiotherapy resulted in significantly less IQ deterioration than standard radiotherapy [Merchant et al, Pediatr Blood Cancer, 2008].	The referenced study collected radiation dose data for 40 patients, estimated dose that would have been received with PBRT, and applied a model of cognitive impact. The model suggests PBRT may have a lower cognitive impact for pediatric brain tumors. Comparative trials on this outcome are unlikely due to lack of clinical equipoise. The subcommittee recommended coverage of PBT for pediatric tumors.
J	62	Head & Neck Cancers -A meta-analysis evaluating the role of photons and charged particle therapy for sinonasal carcinoma demonstrated improved disease-free survival (DFS) and LC with charged particle therapy; subgroup analysis comparing IMRT and PBRT confirmed that 5-year DFS was significantly higher at five years for patients receiving PBRT (72% versus 50%) [Patel et al, Lancet Oncol 2014].	See also comment A9 regarding Patel 2014. PBT for sinonasal carcinoma is recommended for coverage.
J	63	Breast Cancer-A recent population-based study of 2168 woman, [Darby et al N Engl J Med. 2013] found that collateral radiation exposure to the heart during breast cancer X-ray treatment increases the subsequent rate of ischemic heart disease. PBRT can significantly reduce this exposure. Macdonald et al reported the results of a prospective trial of protons after mastectomy for patients with excellent clinical outcome and significant reduction in heart dose when compared to X-rays. [Macdonald et al Int J Radiat Oneal Bioi Phys. 2013]	See comments A10, A11.
J	64	The Cost of Protons for Children-The cost-effectiveness of PBRT in pediatric malignancies has been explored. We would highlight that although PBRT is more resource-intensive to deliver upfront, it is aligned with the judicious use of health care dollars. Lundqvist et al examined the cost of proton beam radiotherapy for childhood medulloblastoma and found that proton therapy was associated with €23,600 in cost savings and 0.68 additional quality-adjusted life-years per	Lundkvist 2005 is discussed extensively in the WAHTA report used for this CG.

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		patient. The analyses showed that reductions in IQ loss and GHD contributed to the greatest part of the cost savings and were the most important parameters for cost-effectiveness. [Lundqvist et al, Cancer 2005]	
J	65	We urge the Commission to support the coverage of proton therapy for a broader range of cancers and specifically highlight pediatric tumors and welcome the opportunity to serve as an on-going resource as you are assessing this promising cancer therapy option for Oregonians. Thank you for taking time to review this letter.	Thank you for your comments.
K	66	Dear Regence, I am writing to encourage you to examine your policy of not covering Proton Therapy where it has been proven effective, such as in the treatment of liver cancer. I think that all insurers should now be offering coverage for this approach to treating disorders in which it has been shown to be efficacious.	Commenter addresses Regence; nevertheless, thank you for your comments.
L	67	We are faculty members of the Department of Radiation Oncology at the University of Washington. The majority of our head and neck patients are not treated with protons; we use it selectively in cases where we feel there is a benefit over standard forms of radiotherapy. While the Seattle Cancer Care Alliance Proton Center is one of the sites where our group practices, we have no equity interest in the center. There is no financial incentive for us to treat patients there as opposed to other sites. We would like to call your attention to the following literature:	Thank you for your comments. WAHTA included two very small poor-quality comparative cohort studies for head & neck cancer. References submitted by this commenter are all non-comparative. It may be that individual tumor types are rare enough and proximal tissues sensitive enough that comparative studies are not feasible. Following public comment and expert testimony, the subcommittee recommended coverage of PBT for certain head and neck cancers; namely, skull-base tumors, paranasal sinus tumors, and juxtaspinal tumors.
L	68	Skull Base Tumors One of the challenges with skull-based tumors is their proximity to the brainstem and optic structures, which can be dose-limiting organs when treating relatively radio resistant histologies such as chordomas and chondrosarcomas. With conventional photon radiotherapy, dose is limited to 55 Gy and associated with an inferior local control (LC) rate of	Commenter notes poor local control rate when dosimetry is limited by nearby organs. Reference 1 is a review article from 1999. Direct comparative

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<tr><td></td><td></td><td>approximately 30-50% (1). In contrast, LC for these skull-based chordomas and chondrosarcomas is higher with charged particle therapy, as summarized in the following table:</td><td>studies are not provided. HTAS recommends skull base tumors for coverage.</td></tr>
<tr><td>L</td><td>69</td><td>TABLE: LC Rates for Sarcomas or Chordomas of the Skull Base treated with α-Particles or Protons
<table>
<tr><th>Facility</th><th>Chordoma</th><th>Chondrosarcoma</th><th>Sarcoma (other)</th></tr>
<tr><td>LBNL (2)</td><td>63%</td><td>78%</td><td>58%</td></tr>
<tr><td>HCL-MGH (1,3)</td><td>59%</td><td>99%</td><td></td></tr>
<tr><td>LLUMC (3)</td><td>76%</td><td>92%</td><td></td></tr>
<tr><td>Orsay (4)</td><td>83%</td><td>90%</td><td></td></tr>
<tr><td>Tsukuba (5)</td><td>46%</td><td></td><td></td></tr>
<tr><td>PSI (6)</td><td>88%</td><td>100%</td><td></td></tr>
</table></td><td>Reference 2 is a 1994 case series of 223 patients treated from 1977-1992.

Reference 3 is a 1995 case series of 204 patients treated from 1975-1993.

Reference 4 is a 2001 case series of 45 patients treated from 1995-1998.

Reference 5 is a 2004 case series of 13 patients treated from 1989-2000.

Reference 6 is a 2005 case series of 29 patients treated from 1998-2003.

No comparative data are identified.

The subcommittee heard testimony that comparative data in this setting are not feasible. Treatment decisions are made by dosimetry calculations and these can be impacted by exposure of nearby structures. PBT for skull base tumors is recommended for coverage.</td></tr>
<tr><td>L</td><td>70</td><td>In the Loma Linda University Medical Center (LLUMC) series, all "small and medium size" tumors without brainstem involvement were controlled with only a 7% incidence of late toxicity. (3)</td><td>This case series of 204 patients was conducted from 1975-1993</td></tr>
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			and may not represent contemporary practice and technology.
L	71	Nasopharyngeal Carcinomas Compared with conventional radiotherapy, use of protons for treatment of nasopharyngeal carcinomas is associated with less dose to the optic structures, brain, and inner ears.	Thank you for your comments.
L	72	Lin et al reported on 16 patients with recurrent nasopharyngeal cancer who underwent proton reirradiation to 59.4-70.2 CGE after failing initial photon radiotherapy treatment to 50.0-88.2 Gy (7). Progression-free survival (PFS) was 50% at two years. Among those patients with "optimal" coverage, 2-year PFS was 83%. No patient had significant CNS toxicity.	Reference 7 is a 1999 case series of 16 patients. No comparative data are identified.
L	73	Chan et al reviewed outcomes for 17 patients with newly-diagnosed T4N0-3 nasopharyngeal tumors treated at either HCL-MGH or the Francis H. Burr Proton Therapy Center with combined proton and photon radiotherapy (8). The median prescribed dose was 73.6 CGE. Ten patients received induction and/or concomitant chemotherapy. LC and overall survival at 3 years were 92% and 74%, respectively.	Reference 8 is a 2004 case series of 17 patients treated from 1990-2002. No comparative data are identified.
L	74	Dosimetric comparative studies have demonstrated improved tumor coverage and conformality with intensity modulated proton therapy (IMPT) as compared to IMRT techniques. Given superior conformality, "avoidance structures" such as the spinal cord, inner ear, and middle ear received a 2-3 times lower median dose than with IMPT (9).	Reference 9 is a treatment planning study comparing potential radiation doses in 8 patients using IMRT or PBT. Study looked at planned/hypothetical radiation doses only.
L	75	Paranasal Sinus Tumors The close proximity of paranasal sinus tumors to brain and optic structures make these tumors amenable for proton radiotherapy. Among 14 patients with esthesioneuroblastomas treated with protons at Chiba, Japan, between 1999 and 2005, 5-year actuarial LC was 84% and overall survival was 93% (10).	Reference 10 is a retrospective cohort study of 14 patients treated from 1999-2005 in Japan. No comparative data are identified.
L	76	Chan et al reported on 91 patients with advanced paranasal sinus tumors who received combined photon and proton radiotherapy at the HCL-MGH to a mean dose of 73.6 CGE (11). The 3-year LC was 83% for squamous cell tumors, 91% for carcinomas having neuroendocrine features, 86% for adenoid cystic carcinomas, and 88% for sarcomas.	Reference 11 is a case series of 91 patients treated from 1988-2002. No comparative data are identified.
L	77	Lastly, outcomes among 1186 patients with paranasal sinus tumors treated with photons were compared with 286 patients treated with charged particle therapy in a meta-analysis. Overall survival and disease-free survival at 5 years	See also comment A9 regarding

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		were significantly higher among the charged particle therapy group. Among patients treated with proton radiotherapy versus IMRT, 5-year disease free survival and loco regional control at longest follow-up were higher among the proton radiotherapy group (12).	Patel 2014. PBT for sinonasal carcinoma is recommended for coverage.
L	78	Juxtaspinal Tumors When tumors are invasive or adherent to critical structures such as the vertebral body, spinal cord, or peripheral nerve roots, complete resection is difficult to achieve. Because the tumor is adjacent to the cord, with conventional radiotherapy techniques, dose to the tumor is limited by the cord's tolerance to radiation, 50-55 Gy. The use of protons or other charged particles allows one to wrap the high dose volume around and avoid the spinal cord; tumors can therefore be treated to 70 CGE with proton radiotherapy.	It is noted that radiation of juxtaspinal tumors is limited by tolerance of adjacent spinal cord.
L	79	Among 51 patients with cervical spine chordomas treated at MGH-HCL, LC was 65% (3). Nowakowski et al described a series of 52 patients with juxtaspinal tumors of varying histologies and locations treated with D-particles at the Lawrence Berkeley Laboratory; 16 of these were located in the cervical spine (13). The overall LC was 58% for 36 patients with previously untreated lesions.	Reference 3 is discussed under comment 69. Reference 13 is a case series of 52 patients treated from 1976-1987. No comparative data are identified.
L	80	Oropharyngeal Tumors Using a combination protons and photons in an accelerated fractionation schema, LLUMC treated 29 patients with locally-advanced, oropharyngeal carcinomas (13). The overall, 5-year actuarial loco regional control rate was 84% (88% primary site, 96% neck nodes); 5-year disease-free survival was 65%.	See comment 79.
L	81	Frank et al presented data at the 55th Annual Meeting of the American Society for Radiation Oncology showing that patients with orophalyngeal tumors treated with protons had a substantially lower requirement for feeding tubes during therapy than a comparable group of patients treated with IMRT (20% vs. 48%) and less nausea, emesis, and mucositis. A subsequent report on 15 head and neck cancer patients treated using multifield optimization of IMPT showed only one case of grade 3 mucositis in the posterior oral cavity; there was no grade 2 or higher mucositis in the anterior oral cavity (15).	Reference 15 is a case series of 15 patients, reporting “the first clinical experience and toxicity of multifield optimization (MFO) intensity modulated proton therapy (IMPT) for patients with head and neck tumors.” No comparative data are identified.
L	82	Retreatment of Treatment Failures Management of patients with recurrent head and neck cancer who have failed an initial, radiation based treatment is challenging. Re-irradiation with photons, with or without chemotherapy, is associated with 34-65% grade 3+ toxicity. For	Reference 16 is a 2013 dose-planning study of 7 patients, comparing helical tomotherapy

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		non-nasopharyngeal sites, these serious side effects can include osteoradionecrosis, laryngeal and swallowing dysfunction and carotid artery ruptures (16). IMPT is significantly better than IMRT in terms of normal tissue sparing, particularly in the low to intermediate dose regions (17).	to IMPT. "IMPT was found not to be uniformly superior to HT… comparative dose planning is recommended if both methods are available." The subcommittee heard testimony that comparative dose planning is standard of care and that PBT will be recommended only when comparative dose planning finds it likely to be superior for a given patient. Coverage of PBT is recommended for malignant brain, spinal, skull base, paranasal, and juxtaspinal tumors [whether they are initial or recurrent]
M	83	Dear Commission Members: The American Society for Radiation Oncology* (ASTRO), appreciates the opportunity to comment on the Oregon Health Evidence Review Commission (HERC) Coverage Guidance for Proton Beam Therapy. We are concerned that the HERC Coverage Guidance is overly restrictive, inconsistent with current literature, and will have a detrimental effect on vulnerable populations who derive the most benefit from access to proton beam therapy.	Thank you for your comments.
M	84	Proton beam therapy (PBT) is neither a new nor an experimental technology for treating cancer with radiation. It utilizes proton radiation particles to deliver highly conformal radiation therapy to a specific tumor target area while giving a much lower dose to the normal tissues in the proton beam's path of entry and exit. PBT's reduced radiation dose to healthy tissues can reduce side effects for patients with demonstrated effectiveness in increasing quality of life. To date, scientific evidence exists confirming that PBT is particularly useful in a number of pediatric cancers, particularly those in the brain, as well as for certain adult cancers, such as ocular melanoma, chordoma, chondrosarcoma, and primary hepatocellular carcinoma. Patients with genetic syndromes and those with tumors near the spinal cord with previous irradiation also benefit from the use of PBT. Additional research on other cancer disease sites, such as breast, prostate and lung, is ongoing with NCI-supported clinical trials currently accruing patients in all three disease sites at the more than 14 proton therapy treatment centers around the country.	This information is correct and consistent with the CG report.

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M	85	In June 2014, ASTRO released a PBT Model Policy that identifies cancer diagnoses that meet ASTRO's evidence-based standards that should be covered by private insurers and Medicare. This Model Policy recommends two coverage groups for PBT: 1) patients with specific diagnoses for which PBT has been proven to be effective; and 2) patients with cancer diagnoses where there is a need for continued clinical evidence development and comparative effectiveness analyses for the appropriate use of PBT. For the patients in group two, coverage with evidence development is recommended for patients if they are enrolled in clinical trials or a multi-institutional registry to collect data and inform consensus on the role of proton therapy.	Please see comment 5.
M	86	The HERC Coverage Guidance is especially concerning because it declines to provide coverage for pediatric malignant tumors. PBT is an important treatment option for certain pediatric tumors, since damage to the surrounding normal tissues in children can produce serious long-term side effects on the growth and development of vital organs and tissues. A growing body of literature shows the late effects, quality of life, and cost effectiveness of proton beam therapy on pediatric patients. Randomized studies are not feasible given the general acceptance of PBT for pediatric patients within the expert community. To account for this, research compares these patients to appropriate historical cohorts. These studies are relatively "small" due to low incidence of these diseases; however, data are being collected prospectively for all children in single and multi-institutional databases. (1)	It is noted that comparative studies are unlikely to be conducted in pediatric tumors due to lack of clinical equipoise. The subcommittee recommended coverage of PBT for pediatric tumors.
M	87	Additionally, we are unaware of any coverage policies that deny coverage of PBT for pediatric tumors, and we are concerned that the denial of PBT coverage for pediatric patients will considerably restrict children's access to curative and palliative treatment. ASTRO strongly recommends that HERC extend coverage to include primary or benign solid tumors in children, per the ASTRO PBT Model Policy.	Thank you for your comments.
M	88	PBT has attracted significant attention due to its relative cost, which is usually higher than traditional external beam radiation therapy. However, studies now suggest that proton therapy can be a cost-effective strategy for the management of certain cancers. (2, 3, 4) In one study, proton beam therapy was proven to be associated with higher quality-adjusted life years and lower costs. (5)	The cost studies referenced were considered in the WAHTA report on which our CG is based.
M	89	Furthermore, we are concerned that in developing this coverage guidance, HERC did not consult the opinions of experts in the field nor did they review the full body of evidence surrounding proton beam therapy as an effective form of cancer treatment. We are very surprised that the ASTRO PBT Model Policy, which was carefully developed by leading radiation oncologists and medical physicists and benefitted from balanced input from experts in proton therapy, was not cited as a reference in the HERC Coverage Policy for Proton Beam Therapy.	The coverage guidance process solicits expert input as well as public comment such as this one. Please see comment 5 regarding ASTRO.
M	90	ASTRO is committed to providing evidence-based guidance to payers in the form of recommendations for correct coverage policies for radiation oncology. We encourage HERC to follow the lead of many national private and public insurers by consulting the evidence and following the recommendations in ASTRO's PBT Model Policy when developing coverage policies for PBT. The ASTRO PBT Model Policy is enclosed for your review, in addition to a list of references and	Thank you for your comments.

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		supporting articles.	
M	91	Thank you for your consideration of our comments. Should you have any questions or wish to discuss our concerns further, please contact ASTRO's Director of Health Policy	Thank you for your comments.
N	92	Dear Oregon Health Evidence Review Commission: As a Radiation Oncology faculty member at the University of Washington, I specialize in caring for patients of all ages with central nervous system tumors. A minority of my patients are treated with proton beam therapy. For these patients, proton beam therapy provides the best chance of curing their brain tumors while minimizing significant side effects. Proton beam therapy has no exit radiation dose, which patients would otherwise receive if treated with x-rays. This is especially important in the central nervous system where very low doses of radiation to normal brain can cause neurocognitive decline, hormonal deficits, and secondary malignancies. For spinal cases, low dose radiation to the anterior organs is associated with nausea and lower blood counts in the short term; and heart disease and secondary malignancies in the long term.	Thank you for your comments.
N	93	The Washington Health Technology Assessment recently issued a final report where they universally recommended that proton beam therapy for brain/spinal cancers be covered by state insurance. This was based on finding equal benefit and decreased harm for proton beam therapy over conventional therapy. In addition, many other coverage policies agree with this recommendation, and I urge you to do the same.	The WAHTA evidence report formed the basis for this CG document. Following the evidence report and public comment, the Health Technology Clinical Committee voted unanimously to recommend coverage of PBT with conditions, namely: - Ocular tumors - Pediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing's sarcoma) - Central nervous system tumors (e.g. brain, spinal and paraspinal tumors) - Other non-metastatic cancers with the following conditions: a) Patient has had prior

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			radiation in the expected treatment field with contraindication to all other forms of therapy, and b) At agency discretion Following public testimony and expert input, the subcommittee recommended coverage of PBT for malignant brain and spinal tumors.
N	94	Summary of Evidence *Pediatric central nervous system cancers:* Children have developing tissues that are exquisitely sensitive to radiation. Though long term survival is now achieved in the majority of patients, side effects from radiation therapy can have a profound effect on quality of life in survivors.	Please see comments 59 and 61.
N	95	In a study of patients receiving irradiation for a brain tumor before than age of four, only a third of adult survivors were able to have full-time employment. (1) Modeling of the effect of radiation therapy on IQ predicted a significant decrease in neurocognitive decline for older children as well. (2)	Reference 1 is a case series of 222 children treated from 1958-1995. Reference 2 is addressed in comment 61.
N	96	In a St Jude study of children treated for brain tumors, 94% had resulting growth hormone deficiency, 50% had hypothyroidism, and 43% had adrenal insufficiency.3 Proton therapy can decrease the pituitary dose for many cases.2	Please see comment 61.
N	97	Protons allow for sparing of the cochlea, resulting in lower ototoxicity rates. (4)	Reference 4 is considered in the WAHTA evidence review.
N	98	Finally, a recent study of pediatric patients with retinoblastoma showed that the 10 year cumulative incidence of secondary malignancy was 14% in patients treated with photons versus 0% in patients treated with protons. This supports the conclusion that protons will decrease the risk of secondary malignancy, which is 20.5% in 5 year survivors of childhood cancer. (5)	Reference for the comparative study of retinoblastoma treatment is not provided. Reference 5 is a case series of 14,359 survivors of childhood cancers; the 20.5% figure is correct.
N	99	*Adult low grade gliomas:* Recent multicenter randomized trials have shown median survival for patients with grade II	Reference 6 is a phase III trial

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		gliomas (both astrocytoma and oligodendroglioma) and grade III oligodendroglioma to now be greater than fourteen years with radiation therapy and chemotherapy. (6, 7) However, adult low grade glioma survivors have poor cognitive function when receiving postoperative radiation therapy, which limits their ability to work and decreases their quality of life. (8) A recent prospective phase II trial of proton beam therapy for low grade gliomas showed no evidence of overall decline in cognitive function or quality of life based on neurocognitive assessment and patient questionnaires. (9)	comparing chemotherapy + radiotherapy vs radiotherapy alone in 291 patients. Median survival was not different between groups for the whole cohort. The 14-year figure applies to patients with codeleted tumors only, which was not a predefined subgroup analysis. Reference 7 is an editorial describing long-term follow up results of the same study. Reference 8 is a cross-sectional study comparing self-reported cognitive function in 195 low-grade glioma survivors with 100 low-grade hematological patients and 195 healthy controls. The authors conclude that "Our findings suggest that the tumour itself has the most deleterious effect on cognitive function and that radiotherapy mainly results in additional long-term cognitive disability when high fraction doses are used." Reference 9 is a prospective single-arm cohort study of 20 patients followed for 5 years after proton therapy. No overall decline in cognitive function was detected.

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			Direct comparative data of PBT vs other treatment is not identified.
N	100	*Adult benign brain tumors (e.g. meningioma, vestibular schwannoma, pituitary adenoma):* Multiple series document the outcomes of proton therapy for the treatment of meningioma (10-13), pituitary adenoma (14), and vestibular schwannoma (15). For patients with benign disease and good long term prognosis, proton beam therapy decreases the risk of neurocognitive decline, endocrine dysfunction, and secondary malignancy. (16, 17)	References 10-13 are considered in the WAHTA evidence review. Reference 14 was published after the WAHTA review. It is a case series of 165 patients with functional pituitary adenoma treated from 1992-2012. Reference 15 is a case series of 64 patients treated with stereotactic radiation therapy. It did not discuss proton beam. No comparative data are identified. Reference 16 is a treatment-planning study of 10 patients in which treatment was re-planned with proton radiotherapy and effect differences were estimated based on hypothetical dose. Reference 17 is a similar modeling study in which doses are estimated using 8 different techniques in one standard case.
N	101	*Adult medulloblastoma:* The NCCN guidelines recommend considering proton therapy for craniospinal irradiation for adult medulloblastoma given published data by MD Anderson showing less weight loss and hematologic toxicity for patients undergoing proton therapy compared to photon therapy. (18)	Reference 18 is considered in the WAHTA review.
N	102	*High grade gliomas:* The median survival for glioblastoma multiforme is still roughly one year with chemotherapy and	It is noted that studies of proton

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		radiation therapy. Recent data suggests that increasing the radiation dose for initial treatment or giving a second course of radiation therapy for recurrent gliomas will improve outcomes. However, past efforts to escalate dose or re-irradiate have resulted in considerable toxicity. Thus, we are participating in two national cooperative group NRG Oncology clinical trials, BN001 and RTOG 1205. (19, 20) Both trials use proton therapy with the aim of improving survival for this otherwise devastating disease.	beam for GBM are in progress. Studies in progress will be considered after peer review and publication.
N	103	*Cost effectiveness:* Recent studies that modeled the cost of long term effects of radiation therapy for pediatric patients with brain tumors found that proton therapy is overall cost effective. (21, 22) Indeed, in my practice I find that long term survivors of brain tumors may be cured but have considerable late effects including neurocognitive decline and hormonal deficiency that are costly to the patient in terms of their ability to work and to payers in terms of medical care.	References 21 and 22 are the two papers by Mailhot Vega; please see comment 13.
N	104	I urge the Commission to support coverage of proton therapy for central nervous system tumors and welcome the opportunity to serve as an on-going resource as you are assessing this important cancer therapy option for Oregonians. Thank you for this opportunity.	Thank you for your comments.
O	105	To: Regence It has come to my attention that your insurance does not currently cover proton radiation treatment for all forms of cancer. I am writing to advocate that you at least provide your beneficiaries who have liver cancer, with this coverage. I hope you know that it has proven to be efficacious. Thank you for being responsive to the needs of your beneficiaries.	Commenter addresses Regence; nevertheless, thank you for your comments.
P	106	Dear Oregon Health Evidence Review Commission: On behalf of the Particle Therapy Cooperative Group- Nmih America (PTCOG-NA)1, we respectfully submit comments on Oregon's Health Evidence Review Commission (HERC) Coverage Guidance on Proton Beam Therapy (PBT).	Thank you for your comments.
P	107	While we were pleased to see the strong recommendation for coverage of malignant ocular tumors, we have significant concerns with many of the other recommendations. We were especially surprised and disappointed with the lack of a positive coverage recommendation for pediatric malignant tumors. Because of the strong evidence supporting its use, PBT for pediatric patients is practically universally covered. Additionally, we strongly disagree with your characterization that "PBT is far more expensive than its major alternatives." Recent studies have found that when treating for toxicity and other post-treatment occurrences are considered, PBT has been found to be a cost-effective treatment. We urge you to consider the evidence we provide in this letter in your deliberations.	Available cost-effectiveness data have been considered. The HTAS recommended coverage of PBT for pediatric tumors.
P	108	Evidence on the Effectiveness of PBT for Pediatric Malignant Tumors The proposed coverage guidance gave a weak recommendation for coverage for pediatric malignant tumors, despite the	The HTAS recommended coverage of PBT for pediatric

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		overwhelming consensus on its appropriateness for pediatric patients. We believe eliminating coverage of PBT for pediatric patients is inconsistent with the current state of evidence and would be harmful to a population of patients who would most benefit from the reduced amount of radiation received in the course of PBT treatment.	tumors.
P	109	Due to the growing body of evidence in this area, most payors, regulators and providers support the use of PBT for pediatric patients. The consensus is reflected in the American Society for Radiation Oncology (ASTRO) model policy on PBT which supports its use for primary or benign solid tumors treated in children with curative intent (ASTRO, 2014). (1) Examples of published evidence in this area include a recent study of 54 patients with pediatric rhabdomyosarcoma which found that PBT lowers integral dose and improves sparing normal tissue when compared to IMRT [Ladra, MM et al Radiother Oncol 2014]. (2)	Please see comment 5 regarding ASTRO. Ladra 2014 is a prospective cohort study of 54 patients who received proton therapy; IMRT plans were generated for comparison.
P	110	In another example, a 2012 study of high risk pediatric neuroblastoma found that preliminary outcomes reveal excellent control with proton therapy for this population [Hattagangadi JA, Int J Radiat Oncol Biol Phys, 2012]. (3) While we have cited just two studies, these are consistent with other studies of pediatric patients.	Hattangadi 2012 was considered in the WAHTA document.
P	111	Evidence on the Effectiveness of PBT for Other Sites The proposed guidance concludes, " ... there was insufficient evidence to obtain even a basic understanding of PBT's comparative clinical effectiveness and comparative value." Frankly, we were stunned by this characterization. While we acknowledge (and support) the ongoing development of additional clinical evidence, there is already significant evidence supporting the effectiveness of PBT that this proposed coverage guidance ignores. In addition to the evidence supporting the use of PBT for pediatric tumors, there is significant evidence supporting its use for other tumor sites.	The CG was based on a WAHTA report that came to this conclusion.
P	112	The articles listed below are only from the last 15 months and they reflect the meaningful research being conducted in this area. 2015 • Cuaron JJ, Chon B, Tsai H, Goenka A, DeBlois D, Ho A, Simon P, HugE, Cahlon 0 . Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer. *Radiation Oncology.* Published online March 6, 2015. • Holliday EB, Mitra HS, Somerson JS, Rhines LD, Mahajan A, Brown PD, Grosshans DR. Postoperative proton therapy for chordomas and chondrosarcomas of the spine: adjuvant vs. salvage radiation therapy. *Spine.* Published online January 23, 2015. • Mizumoto M, Oshiro Y, Takizawa D, Fukushima T, Fukushima H, Yamamoto T, Muroi A, Okumura T, Koji T, Sakura H. Proton beam therapy for pediatric patients with ependymoma. *Pediatrics International.* 2015;	Cuaron (2015) is a case series that assessed dosimetry and early toxicity of PBT in 30 patients with metastatic breast cancer. Dosimetry was deemed adequate and toxicity was deemed acceptable. Holliday (2015) is a case series that assessed local control (58%), relapse-free survival (51.9%), and overall survival (93.3%) in 19 patients with

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		DOI:10.1111/ped.12624. • Vega RM, Kim J, Hollander A, Hattangadi-Giuth J, Michalski J, Tarbell NJ, Yock Tl, Bussiere M, MacDonald SM. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer.* Published online January 29, 2015. 2014 • Brower *N,* Gans S, Hartsell WF, Goldman S, Fangusaro JR, Patel N, Lulla RR, Smiley NP, Change JH, Gondi V. Proton therapy and helical tomothrapy result in reduced dose deposition to the pancreas in the setting of cranio-spinal irradiation for medulloblastoma: implications for reduced risk of diabetes mellitus in long-term survivors. *Acta Oncol.* 2014 Nov: 1-5. • Frank SJ, Cox JD, Gillin M, Mohan R, Garden AS, Rosenthal DI, Gunn GB, Weber RS, Kies MS, Lewin JS, Munsell MF, Palmer MB, Sahoo N, Zhang X, Liu W, Zhu XR. Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation to practice. *Int J Radiat Oncol Bioi Phys.* 2014 Jul 15;89(4):846-53. • Kesarwala AH, Ko CJ, Ning H, et al. Intensity-modulated proton therapy for elective nodal irradiation and involved-field radiation in the definitive treatment of locally advanced non-small cell lung cancer: a dosimetric study. *Clinical Lung Cancer.* Available online 9 December 2014. • Ladra MM, Szymonifka JD, Mahajan A, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. *J Clin Oncol.* 2014 Oct 20; epub ahead of print. • Ling TC, Slater JM, et al. Analysis of intensity-modulated radiation therapy (IMRT), proton and 3D conformal radiotherapy (3D-CRT) for reducing perioperative cardiopulmonary complications in esophageal cancer patients. *Cancers.* 2014;6(4):2356-2368. • Makita C, Nakamura T, Takada A, Takayama K. Suzuki M, Amazi Y, Kato T, Tsukiyama I, Hareyama M, Kikuchi Y, Daimon T, Hata M, Inoue T, Fuwa N. High-dose proton beam therapy for stage I non-small cell lung cancer: clinical outcomes and prognostic factors. *Acta Oncol.* 2014Oct 7:1-8 (Epub ahead of print). • Patel SH, Wang Z, Wong WW, Murad MH, Buckey CR, Mohammed K, Alahdab F, Altayar 0, Nabhan M, Schild SE, Foote RL. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lance/ Oncol.*2014 Aug; 15(9): I 028-1038. • Schild SE, Rule WG, Ashman JB, Vora SA, Keole S, Anand A, Liu W, Bues M. Proton beam therapy for locally advanced lung cancer: a review. *World J Clin Oncol.* 2014 Oct 10;5(4):568-75. • Sethi RV, Shih HA, Yeap BY, et al. Second nonocular tumors among survivors of retinoblastoma treated with	chordoma or chondrosarcoma treated with PBT. Patients with primary adjuvant radiation therapy had better 2 year LC than those receiving salvage treatment. Mizumoto (2015) is a case series that assessed local occurrence and toxicity in 6 pediatric patients with ependymoma treated with PBT. Simulation showed that PBT reduces dose to normal brain tissue by half compared to photon therapy. All patients were alive at follow up (13-44 mo) and there was no severe toxicity. Mailhot Vega (2015) is a cost-effectiveness study of PBT compared with photon therapy for pediatric patients with growth hormone deficiency.PBT is cost effective in some scenarios based on hypothalamic sparing. Brower (2014) is a case series that assessed dosimetry of PBT compared with 3DCRT and inverse-planned intensity modulated radiation therapy (IMRT) with helical tomotherapy in five pediatric patients with medulloblastoma. PBT resulted in less radiation to the pancreas

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		contemporary photon and proton radiotherapy. *Cancer.* 2014;120(1):126-133. • Thaker NG, Guzman AB, Feeley TW, Jones TM, lncalcaterra JR, Kolom C, Tatum LS, Walters RS, Cantor SB, Rosenthal DI, Garden AS, Gunn GB, Fuller CD, Palmer MB, Frank SJ. Defining the value of proton therapy using time-driven activity based costing. On col Payers 1 (1):22-28,2014. • Yock Tl, Bhat S, Szymonifka J, Yeap BY, Delahaye J, Donaldson SS, MacDonald SM, Pulsifer MB, Hill KS, DeLaney TF, Ebb D, Huang M, Tarbell NJ, Fisher PG, Kuhlthau KA. Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. *Radiother Oncol.*2014 Oct 7. [Epub ahead of print]	than other treatments. Franks (2014) is a case series that assessed toxicity of multifield optimization intensity modulated PBT in 15 patients with head and neck cancer. There were no treatment-related deaths, and with a median follow-up time of 28 months (range, 20-35 months), the overall clinical complete response rate was 93.3% Kesarwala (2015) is a case series that assessed intensity-modulated PBT dosimetry in 20 patients with locally advanced non-small cell lung cancer. All evaluated dosimetric parameters improved significantly with proton plans compared with photon IFRT. Ladra (2014) is a case series that assessed disease control and toxicity of 57 pediatric patients with rhabdomyosarcoma treated with PBT. Five-year LC, EFS, and OS rates were similar to those observed in comparable trials that used photon radiation. Acute and late toxicity rates were favorable. Ling (2014) is a case series that assessed dosimetry of IMRT,

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			3DCRT and PBT in 10 patients with esophageal cancer. Authors conclude proton plans are technically feasible while achieving adequate coverage with lower doses delivered to the lungs and cardiac structures. Makita (2015) is a case series that assessed survival, local control, and toxicity in 56 patients with stage I non-small cell lung cancer treated with two PBT protocols. The three-year overall survival, progression-free survival, and local control rates were 81.3%, 73.4%, and 96.0%, respectively. There were no significant differences in outcomes between the two protocols. Late grade 2 and 3 pulmonary toxicities were observed in nine patients and one patient respectively; no grade 4 or 5 toxicities were observed. Patel (2014) is a systematic review and meta-analysis that compares clinical outcomes from PBT and charged particle therapy. Forty-one case series studies were included that reported on overall survival, disease-free survival, and local control. None of the included

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			studies were comparative. The review found higher overall survival and locoregional control for charged particle beam than PBT at longest follow-up (not defined), and no difference in disease-free survival at longest follow-up between groups. Schild (2014) is a narrative review on the use of PBT as part of a multi-modal treatment program for patients with locally advanced lung cancer. "This review was written for the non-radiation oncologist who wishes to understand the use of proton beam therapy (PBT) for locally advanced lung cancer. One randomized study is being performed and another is planned to clarify the differences in outcome for PBT compared to XRT. Newer forms of radiotherapy such as PBT should positively impact lung cancer patients." Sethi (2014) is a retrospective case series that assessed recurrence rates in 86 patients with retinoblastoma treated with PBT or photon radiotherapy. The 10-year cumulative incidence of RT-induced or in-field second

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			malignancies was significantly different between radiation modalities (proton vs photon: 0% vs 14%; P = .015). The 10-year cumulative incidence of all secondary malignancies was also different, although with borderline significance. Thanker (2014) is a time-driven activity-based costing study of two patients with advanced head and neck cancer treated with IMRT and intensity-modulated PBT. It is published in a non-peer-reviewed journal. Authors conclude that the episodic cost of care using IMPT was less costly and of higher value than IMRT. Yock (2014) is a case series that compared parent proxy health-related quality of life scores of 57 pediatric brain tumor patients treated with PBT with those of 63 pediatric brain tumor patients treated with photon beam radiation. The total core HRQoL score for the PRT-C, XRT-C, and normative population differed from one another and was 75.9, 65.4 and 80.9 respectively (p=0.002; p=0.024; p<0.001). HRQoL of pediatric brain tumor survivors

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			treated with PRT compares favorably to those treated with XRT and similar to healthy controls. The HTAS recommended coverage of PBT for pediatric tumors based on reviewing the limited evidence, expert testimony, and the lack of clinical equipoise that means future trials are unlikely to be conducted.
P	113	For further evidence, we highlight the multiple national guidelines that support the use of proton therapy. The National Comprehensive Cancer Network (NCCN) guidelines, the previously cited ASTRO model policy for proton therapy, and the model policy on coverage of proton beam therapy from the National Association of Proton Therapy (NAPT) both approve of the use of proton therapy for certain patients. The basis for these national guidelines is the growing body of evidence supporting the use of proton therapy for positive long-term treatment outcomes and quality of life for oncology patients. The weight of this evidence is reflected in the numerous Medicare contractors and private payors policies that provide coverage for PBT for a number of anatomical sites.	The guidelines cited are included in the CG document, with the exception of the NAPT. Staff were unable to identify guidelines via search of the NAPT website.
P	114	*PTCOG-NA urges you to* postpone finalizing *this coverage guidance and reconsider your methodology of reviewing clinical evidence. We offer the assistance of our clinical leadership to assist you with any review.*	Thank you for your comments.
P	115	Evidence on the Cost Effectiveness of PBT An overarching benefit of PBT versus photon therapy is its precise targeting that spares very sensitive adjacent normal tissue, resulting in reductions in toxicity and other negative occurrences post-treatment. We are very concerned that you failed to consider these benefits. A study published in *Cancer* [Mailhot Vega, RB et al, *Cancer* 2013] found that by avoiding years of costly side effects, PBT can be cost-effective for children with medulloblastoma.	Please see comment 13.
P	116	An example of this more comprehensive analysis is a recent study issued by MD Anderson Cancer Center and presented at the October 2014 meeting of PTCOG-NA (manuscript under development). The study found that the cost of PBT when used for accelerated partial breast irradiation to decrease overall treatment time and toxicity, was estimated at $13,833. Results of the study suggested that the cost of proton therapy is similar to other types of radiation.	Commenter references unpublished data; new published evidence will be considered as the CG enters re-review every 2 years.

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P	117	*PTCOG-NA strongly recommends that you include studies that consider cost of toxicity and other post-treatment conditions that can occur and which certainly impact costs and the quality of life of the patient.*	Thank you for your comments.
P	118	While we appreciate the opportunity to submit comments, we felt very limited in our ability to communicate to you due to the severe limitations on written (1000 word) and oral (3 minutes) comments. We believe the current process may stymie public input. *PTCOG-NA urges you to reconsider these guidelines.* Should you have any questions, please do not hesitate to contact me	Thank you for your comments.
Q	119	Dear Oregon HERC, I write this letter requesting your consideration in the coverage of proton therapy for prostate cancer.	Thank you for your comments.
Q	120	Proton therapy has been in clinical use in the US since the 1970s. There is a long track record establishing safety and efficacy in patients with prostate cancer over decades of experience. Due to the unique physical characteristics of proton beam radiation (PBT), proton therapy is associated with less dose to surrounding normal tissues in the pelvis (e.g. rectum, bladder) than photon/x-ray IMRT. It allows safe delivery of radiation to the prostate while minimizing side effects.	This is correct and consistent with the background information.
Q	121	Two phase III randomized studies established that protons are a safe and effective means to deliver dose-escalated radiotherapy, the current standard of care in prostate cancer. One study by Massachusetts General Hospital (MGH) randomized patients with prostate cancer to a higher dose proton boost versus lower dose x-ray boost to the prostate following pelvic radiation with xrays. (1) Another study by MGH and Lorna Linda randomized patients with prostate cancer to a higher dose versus lower dose proton boost in combination with x-ray radiation. (2) Both trials showed an improvement in local control with the higher dose proton boost with a very low risk of GU or GI complications.	References 1 and 2 are considered in the WAHTA report.
Q	122	A number of single institutional experiences have also reported excellent long term outcomes with proton therapy. Loma Linda reported a series of 1255 patients with prostate cancer treated with either protons or a combination of x-rays and protons. (3) Survival rates were excellent, and the risk of severe GU or GI complications was extremely low.	Reference 3 is a retrospective cohort study of 1255 patients treated with proton radiation therapy from 1991-1997. Authors concluded that disease-free survival rates were comparable with other forms of local therapy. Authors also concluded that "No difference was seen in toxicity between those treated with combined protons and photons (11 of 731) and those with protons alone (6

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			of 524; p = 0.52).
Q	123	More recently, University of Florida reported their 5-year control rates from 3 prospective PBT trials for prostate cancer: 99%, 99%, and 76% in low, intermediate, and high risk patients, respectively. Among 211 patients, only 1-2% experienced serious late toxicity. These results compare very favorably with published results for IMRT. (4)	Reference 4 is a report of three prospective trials encompassing 211 prostate cancer patients. The data on control rates are correct. Rates of grade 3 GI toxicity were 1.0% and rates of grade 3 urologic toxicity were 5.4%. Within-trial comparative data are not available; commenter is referencing historical IMRT data from other publications.
Q	124	An advantage of PBT is decreased exposure of normal pelvic tissues to low to moderate dose radiation (0-50 Gy). Low-dose radiation to pelvic structures is associated with bowel and bladder urgency, frequency, erectile dysfunction and secondary cancers. (5). These side effects can drastically influence a patient's quality of life (QOL).	Reference 5 is a retrospective questionnaire study of bowel, urinary, and sexual function in 65 patients who received external beam radiation therapy for localized prostate cancer. Within-trial comparative data are not available.
Q	125	No randomized, prospective studies exist comparing IMRT and PBT. Several attempted retrospective comparisons have been conducted using large, national databases including SEER, but these studies suffer from major weaknesses including lack of granular details on side effects such as rectal urgency, poor surrogates for measures of GI toxicity, and comparison based on historical cohorts of small numbers of patients treated with now outdated proton therapy techniques/technology. In one QOL study comparing men treated with IMRT versus PBT, there was less rectal urgency and frequency in men treated with PBT than IMRT. (6)	It is noted that prospective randomized studies exist. Reference 6 is a comparison of QOL data from two different cohort studies, 1243 men receiving PBT and 204 men receiving IMRT. There were **no differences in QOL summary scores** between the IMRT and PT cohorts during early follow-up (up to 2-years). Response to individual questions suggests

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			possible differences in specific bowel symptoms.
Q	126	Decreases in testosterone, the major male hormone responsible for sex drive and stamina, can adversely affect patient QOL. Minimizing low-dose radiation to the pelvis with PBT has been found to translate into improved ability to maintain normal testosterone levels in patients after treatment compared with x-rays. (7)	Reference 7 is included in the WAHTA report.
Q	127	Lastly, decreasing integral radiation dose to the body is associated with a reduced risk for secondary cancers. This is particularly important for younger men seeking an alternative to surgery. In a matched-cohort study that included 33% of men treated for prostate cancer, PBT led to a 50% reduction in incidence of secondary cancers compared to photon-based radiation. (8)	Reference 8 is included in the WAHTA report.
Q	128	We recognize the importance of generating high level-evidence confirming the benefits of PBT in prostate cancer treatment. We are participating in the ongoing multicenter "PartiQOL" randomized trial comparing IMRT vs protons for prostate cancer. Clinical trials like PartiQOL will help quantify the degree of improvement in patient-reported quality of life with PBT over IMRT. In addition, all of our prostate cancer patients are enrolled on a prospective multicenter clinical registry capturing patient reported QOL measures before and after treatment as well as disease control outcomes.	Studies in progress will be considered following publication.
Q	129	This need for continued clinical evidence development (CED) and comparative effectiveness data is recognized by the current ASTRO national model policy for PBT. (9) Under this policy, enrollment in an IRB approved multi-institutional patient registry that adheres to Medicare requirements for CED is considered an indication for proton therapy that should be covered by an insurance carrier. These important trials cannot not be completed if PBT is not covered.	Regarding ASTRO, please see comment 5. Regarding CED, please see comment J57.
R	130	To Whom It May Concern: This letter is in regards to the Oregon Health Evidence Review Commission coverage guidelines for proton beam therapy. As an assistant professor in the department of radiation oncology at the University of Washington, I sub-specialize in breast cancer and would like to comment on the use of proton beam therapy for breast cancer.	Thank you for your comments.
R	131	Proton beam therapy is currently being used in the treatment of breast cancer in many proton centers across the country. The largest, single-institution experience to date using proton beam therapy for breast cancer comes from Loma Linda, where at last publication in 2014, one hundred women with *early stage breast cancer* had been treated with proton beam therapy following surgery (lumpectomy) as part of breast-conserving therapy. (1) When compared with 3-dimensional conformal photon plans for partial breast irradiation, Bush *et al.* reported a significant reduction in exposure to surrounding normal breast tissue with proton beam therapy that led to improved cosmetic outcomes. (2) There was also nominally lower radiation dose to the lung and heart with proton.	Data from the Loma Linda trial are considered in the WAHTA report. Reference 1 was published after the WAHTA report and reports 5-year follow up data on this phase 2 trial of 100 patients; results are not significantly different from prior

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			publications.
R	132	More recently proton beam therapy has been investigated in *locally advanced breast cancer*. The initial experience from Massachusetts General Hospital was published in 2013 and reported on stage III breast cancer patients that were irradiated with protons after mastectomy to the chest wall and regional lymphatics. (3) A comparative dosimetric analysis between proton and photon plans demonstrated substantial reductions in both lung and heart exposure as defined by well-established metrics for those organs at risk. *In addition, there was improvement in prescription dose coverage to the areas at risk*, i.e. chest wall and regional lymphatics received adequate doses. (4) Acceptable acute toxicity (dermatitis and fatigue) was reported. A separate multi-institutional dosimetric study that compared treated photon/electron plans with created proton plans (in press for publication at the time of this letter) confirmed these findings and found superior chest wall and lymphatic coverage and superior normal tissue avoidance in the proton plans.	See comment A11.
R	133	Currently, there has been little experience in salvage or palliative treatment with proton beam therapy for breast cancer. However, future investigation of its use in the setting of local breast recurrence after previous breast conservation therapy (lumpectomy followed by radiotherapy) is worthwhile, particularly given that the current standard of care is mastectomy for these women. If repeat breast preservation can be safely achieved by utilizing proton beam therapy (via less repeat exposure to previously irradiated breast tissue), this can have a significant impact on quality of life.	No additional evidence is supplied.
R	134	No recent cost-effectiveness analyses exist for breast cancer treated with proton beam therapy. However, given the preliminary data described above including lower dose to the heart, lungs, without compromise of target volume coverage, there are potential savings associated with decreased long-term toxicity such as cardiac disease, lung disease and poor cosmetic outcomes. The draft coverage guidelines reference a Swedish study from 2005 that can serve as a guideline for future analyses, but an updated study with current costs in the United States and new information regarding radiation dose-effect relationships is necessary. Cost comparisons have been performed between proton beam therapy and alternative radiotherapy methods for accelerated partial breast irradiation, particularly single-entry catheter based systems that utilize high-dose rate brachytherapy as the radiation source. An up-to-date cost comparison can reveal whether there is still a cost advantage with proton beam therapy when using updated (lowered) reimbursement of single-entry catheter techniques.	No additional evidence is supplied.
R	135	In summary, I believe that the use of proton beam therapy for breast cancer is promising and has provided a significant benefit to the women we have treated. Many others will benefit from proton beam therapy when it becomes a standard treatment option.	Thank you for your comments.
S	136	Dear Oregon Health Evidence Review Commission: I am a board certified Radiation Oncologist on the faculty of the University of Washington and specialize in the treatment of gastrointestinal cancers. I am writing to you because I utilize	Thank you for your comments.

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		proton beam therapy (PBT) in select patients who may benefit from this technology. Patients with gastrointestinal cancers frequently require multimodality treatments (surgery, chemotherapy, radiation therapy) that are curative. However, these may come at the cost of significant early and late side effects that not only impact patients' quality of life but are also costly to health care systems. Key reasons why radiation therapy for gastrointestinal (GI) cancers is so toxic are the close proximity of critical normal GI organs and their high sensitivity to the damaging effects of radiation therapy.	
S	137	PBT has the unique property of eliminating exit radiation dose that patients would otherwise receive if treated with conventional x-rays. This is especially important in the gastrointestinal system where low to moderate doses of radiation to normal liver, stomach, and bowel cause numerous and potentially debilitating GI side effects, which include but not limited to nausea, vomiting, diarrhea, and liver failure.	This information is correct.
S	138	I urge the Commission to consider the following additional information and data when reviewing their coverage guidelines for GI cancers: Liver cancers In accordance with the recent ASTRO Model Policy for PBT, primary liver cancers are supported as medically necessary when treated in a hypofractionated regimen based on meeting the medical necessity requirements of PBT and on published clinical data. The liver is one of the most highly radiation sensitive organs in the body; low to moderate doses of radiation have a profound impact on the normal function of this organ, particularly when the liver is cirrhotic (scarred). PBT allows for safe radiation dose escalation to liver tumors, which has been shown in prospective studies to result in improve survival outcomes. (1)	Please see comment 5.
S	139	In addition to the prospective studies of PBT as detailed by the HERC, a recently published systematic review and meta-analysis compared data across 70 observational studies and demonstrated that compared to conventional photon radiotherapy, PBT had significantly superior 5-year overall survival (RR 25.9), progression-free survival (RR 1.86), and locoregional control (RR 4.3). (2) PBT also had significantly less severe acute and late toxicities (6.1% vs. 20% and 2.5% vs. 6.9%, respectively) compared to photon radiotherapy. Notably, hepatic toxicity, which is often highly morbid, life-threatening, and costly, was lower in PBT versus photon treated patients (3.1% vs. 9.9%).	Reference 2 is a systematic review and meta-analysis as described by the commenter. This was published after the WAHTA report. Carbon-ion therapy was included in the same group as PBT under the category of "charged particle therapy." Survival rates were better than conventional radiotherapy but similar to SBRT.
S	140	Furthermore, due to its dosimetric advantages, PBT allows for hypofractionated treatment, particularly for large liver	Commenter describes a scenario

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<tr><td></td><td></td><td>tumors that would not be amenable to conventional fractionation of photon radiotherapy: instead of delivering 40 fractions (8 weeks) of conventionally fractionated photon radiation, PBT can be safely delivered in only 15 fractions (3 weeks) with biologically equivalent doses. As shown in the table below, when using Medicare reimbursement rates (professional and technical fees), PBT results in cost savings of approximately 30% when compared to IMRT in this setting: $21,665.63 versus $30,678.93, respectively.
<table>
<tr><th colspan="2">IMRT (40 fractions)</th><th colspan="2">PBT (15 fractions)</th></tr>
<tr><td>1 New patient visit</td><td>99205</td><td>1 New patient visit</td><td>99205</td></tr>
<tr><td>1 Prescription</td><td>77263</td><td>1 Planning sim</td><td>77014</td></tr>
<tr><td>1 Sim</td><td>77290</td><td>1 Complex sim</td><td>77290</td></tr>
<tr><td>1 Verification sim</td><td>77280</td><td>1 3D sim</td><td>77295</td></tr>
<tr><td>1 IMRT plan</td><td>77301</td><td>1 Dosimetry calculations</td><td>77300</td></tr>
<tr><td>1 IMRT MLC Device</td><td>77338</td><td>1 Special dosimetry plan</td><td>77331</td></tr>
<tr><td>1 Immobilization Device</td><td>77334</td><td>4 Complex treatment devices</td><td>77334</td></tr>
<tr><td>8 Weekly mgmt</td><td>77427</td><td>4 Apertures/compensators</td><td>77334</td></tr>
<tr><td>8 Physics QA</td><td>77336</td><td>3 Physics QA</td><td>77336</td></tr>
<tr><td>40 IMRT treatments</td><td>G6015</td><td>2 Special physics consults</td><td>77370</td></tr>
<tr><td>6 Films</td><td>77417</td><td>Special treatment procedure</td><td>77470</td></tr>
<tr><td>7 Basic dosi calcs</td><td>77300</td><td>15 IGRT</td><td>G6002</td></tr>
<tr><td>40 CTs</td><td>77014</td><td>15 PBT treatments</td><td>77523</td></tr>
<tr><td>1 Follow-up visit</td><td>99213</td><td>1 Follow-up visit</td><td>99213</td></tr>
<tr><td>Total Cost</td><td>$30,678.93</td><td>Total Cost</td><td>$21,665.63</td></tr>
</table></td><td>in which higher doses can be delivered more efficiently with PBT for liver cancer; published citation is not provided and source of this table is not cited.</td></tr>
<tr><td>S</td><td>141</td><td>Pancreatic cancers

The Commission did not specifically include the review of evidence of PBT in pancreatic cancers. Radiation treatment with concurrent chemotherapy for pancreatic cancer is associated with significant GI toxicity. With conventional radiation, severe acute GI toxicities occur in up to 20% of patients, which can often be treatment-limiting and</td><td>WAHTA identified no comparative studies of the clinical effectiveness of primary PBT in gastrointestinal cancers. Pancreatic cancer data were</td></tr>
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		compromise full completion of treatment. (3)	considered under the category of gastrointestinal cancers. Recommendation is not to cover based on insufficient evidence.
S	142	Dosimetric data as well as phase I clinical data demonstrate that PBT for pancreatic cancer is feasible, tolerable, and safer than with photon therapy. A dosimetric analysis of proton and photon plans for the adjuvant treatment of pancreatic cancer from the University of Florida showed superior small bowel and stomach sparing with PBT. (4)	Commenter notes Phase I clinical data, which was not considered in the CG report. Evidence development for pancreatic cancer is ongoing and will be considered in future updates of the CG.
S	143	A phase I/II study of 50 patients with locally advanced pancreas cancer used 3 dose fractionation schemes of PBT depending on the location of the tumor in relation to other GI structures with concurrent. They found excellent efficacy compared to historical controls of locally advanced pancreas cancer (1-yr local progression free survival 82%, progression free survival 64%, overall survival 77%). (5) The toxicities were low compared to the above mentioned photon based regimens with acute Grade 3 and higher rates as follows: nausea/vomiting 8%, anorexia 8%, weight loss 5%, and fatigue 3%.	Reference 5 is considered in the WAHTA evidence review.
S	144	More recent data from University of Florida and University of Pennsylvania provide additional data that PBT is better tolerated than photons. Nichols et al. from University of Florida demonstrated no grade 3 toxicities or treatment interruptions due to toxicity in 22 patients treated with PBT and concurrent chemotherapy. (6) At the University of Pennsylvania, 13 patients with pancreatic cancer treated with concurrent chemotherapy and proton PBT were compared to a cohort of patients treated during the same time period with photon radiotherapy to similar doses: 24% of the photon patients experienced grade 3 toxicity, whereas only 8% of the PBT cohort had this grade of toxicity. (7)	Reference 6 is considered in the WAHTA evidence review. Reference 7 is a non-randomized comparative study of 13 patients who received proton chemoradiation therapy versus a concurrent cohort of 17 patients who received photon therapy. Rates of toxicity were similar.
S	145	*In summary, there are adequate data from multiple institutions that demonstrate the safety and efficacy of PBT for liver and pancreatic cancers. The reduction in treatment-related toxicities with PBT compared to photon treatment also has the potential to result in cost-savings in these challenging diseases. I urge the Commission to support the coverage of PBT for liver and pancreatic cancers. I welcome the opportunity to serve as an on-going resource as you are assessing*	Thank you for your comments.

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		this important cancer therapy option for Oregonians.	
T	146	In 2011, I was diagnosed with Non-Hodgkins's Lymphoma (NHL) of the Central Nervous System with a mass found per MRI and CT Scan in the L) parietal dura of the brain & inoperable). I was told this is a rare mass found in only 3% of the population of those with NHL. After numerous lumbar punctures and samples of spinal fluid, bone marrow biopsies and finally an Craniotomy for an open biopsy, I began mega dose chemotherapy over a nine month period. At completion and for 12 months I was considered in remission. But after 14 mo MRI check up, they discovered that the mass was returning. At that point, I was given my options of Radiation (radiotherapy with standard Photons) with all it's side affects that would probably include blood brain barrier penetration leaving me with possible irreversible neurological damages, not to mention the probable return of the mass again. There IS limited control with the use of the Photon beams.	Thank you for your comments.
T	147	Or I could endure another long regime of chemo, this time with IT therapy (Intrathecal). Of which there are often high grade toxicities of blood, liver or renal systems). Especially in folks over 60 years of age. Wow, what a choice! (NOT)	Thank you for your comments.
T	148	Then, trying to take all this in for a few days, and pretty much deciding not to do any more treatments, I received a call from my Neuro Oncologist at UW Med Center, stating he had just talked to a specialist at the SCCA Proton Center (new to Seattle about a year before) about my case (my mass was wide but very shallow) and the doctor was interested in using their newest form of therapy called Pencil Beam Scanning (the PBS had only been available for a couple of months at that time). He went on to explain that PBS is higher degree of precision of the Proton Beam with overall minimal exposure and radiation to healthy tissues surrounding the mass. So, I spoke with my family and doctors and decided to take a chance. Then I did my research and discovered that Proton Therapy has been around for 25 years in the U.S. and a few other countries and that it was shown to be effective in treating many types of tumors, including cancers of the brain, CNS, head, neck, prostrate, lung and GI system, as well as cancers that cannot be removed (or completely removed) by surgery or chemo. I was again hopeful.	Thank you for your comments.
T	149	You don't know what it means, or feels like to have someone tell you you're NOT going to have to do the intense treatments that make you feel miserable day after day, to miss family functions or not being able live your life as normally as you'd like.	Thank you for your comments.
T	150	Feb 10, 2014, the first day I entered the Proton Center in Seattle, I felt like I had 'come home' to a new family of folks who are there to help all their patients feel comfortable in their stress-free and friendly environment, as anywhere I had ever been. The team of radiologists were 'my' team and treated me with respect, humor and a positivity beyond belief. I felt I could share my concerns, emotions and joys with them all. I cried when I had finished my regime of treatments, knowing I wouldn't be seeing them every day again. By the way, my only side affects included some tiredness and hair loss of the area radiated (which has since grown back) and missing 'my team' !	Thank you for your comments.

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T	151	Well, that was a year ago, and after my MRI last week, I am still mass free and as my docs put it, I have a 'beautiful brain' once again. This would not be the case with the other choices given to me. My daily life during the treatment did not change and I continued to enjoy daily activities. I can also look forward to the fact that the protons therapy reduces a reoccurrence or secondary mass. I can also live without the thought of residual neurological side affects later in my life.	Thank you for your comments.
T	152	The facility itself is a 'step into the future' kinda place. The center meets all needs of their patients, not just the amenities of the building but the non medical support needed especially if you are away from home, including housing, transportation and entertainment in the area, etc. Always supportive in every way.	Thank you for your comments.
T	153	Being a retired nurse, I can honestly say I have never had a more positive medical experience than that of SCCA Proton Center in Seattle. Believe me, it's different when you're on the receiving end of medical care!	Thank you for your comments.
T	154	I have recommended it to those I know with medical issues that would benefit from Proton Therapy. I'm happy to say that their treatments and positive experiences have been the same as mine. We are blessed to have this 'state of the art' facility in our part of the country. The need is great for more compassionate and successful treatments of all types of cancers. It will definitely be the only way of doing radiation therapy in the near future.	Thank you for your comments.
T	155	I truly feel it would be a disgrace to deny countless lives, the quality (with nil side affects) and compassionate treatment found in Proton Therapy. Please consider SUPPORTING the use of Proton Therapy. It's here to stay. Maybe you would need it someday! Would you want it to be denied to you or a loved one? A true believer in compassionate and quality care!	Thank you for your comments.
U	156	Hello, I chose proton therapy because it has low risk of side effects such as incontinence, impotence and bowel urgency. I also chose proton therapy because I can go to work every day and work a full day's work. I have not missed a single day's work during my treatment. I have been able to perform my work normally with some minimal impact, such as some minor urinary urgency. I would absolutely recommend proton therapy for anyone for whom this is a valid therapy. The impact to my body has been minimal. The treatment here at the SCCA Proton Center in Seattle has been very professional, and my wife and I both felt very encouraged by the whole process, from intake through the daily treatments and the weekly meetings with nurses and my oncologist.	Thank you for your comments.

ID	#	Comment	Disposition
V	157	Please support proton radiation for liver cancer and other cancer where less tissue damage is critical to success of treatment. Thank you	Thank you for your comments
W	158	Dear Oregon Health Evidence Review Commission: I am a Radiation Oncologist on the faculty of the University of Washington and Seattle Children's Hospital. A majority of my patients are children with cancer, and I treat more children with cancer than any other radiation oncologist in the Northwest. About half of my patients are from the Seattle area, and the other half come from other parts of Washington, Alaska, Oregon, Montana, Idaho, and British Columbia.	Thank you for your comments.
W	159	The lack of exit dose with proton radiation can be critical for providing the optimal radiation therapy for children with developing bodies. It allows the patient to receive the maximum efficacy of treatment with decreased acute and late effects. On 11 July 2014 the Washington Health Technology Assessment adopted its final decision to recommend universal coverage for pediatric cancers.	This information is correct.
W	160	Nonetheless the best modality of radiation for each patient is individually assessed. I have treated two children from Oregon with proton therapy; however; I have recently supported the decisions by local Oregon radiation oncologists to treat with photon therapy rather than have them travel for proton therapy.	Thank you for your comments.
W	161	I am a member of the Children's Oncology Group (COG), the principle US entity for clinical research about pediatric cancers. It is noteworthy that most clinical trials that call for radiation other than whole brain radiation (including trials for most brain, Ewings, and rhabdomyosarcoma) allow for the clinician to choose the modality of radiation-proton or photon; it is not a study question on any COG clinical trial.	Thank you for your comments.
W	162	It is also noteworthy that even in somewhat resource-constrained, more centrally organized health systems, proton therapy for pediatric patients is increasingly accepted. For example, Britain's National Health Service is constructing two proton facilities that will treat children.	This is correct.
W	163	It is rare for a pediatric patient not to receive insurance coverage for proton therapy, either with public or private insurance. I urge you to continue support for Oregon pediatric patients to receive proton therapy, particularly when there is consensus between the Oregon radiation oncologist and the proton radiation oncologist.	Thank you for your comments.
W	164	Other clinicians will focus on the benefits of treating lymphoma (including pediatric lymphomas) with proton therapy, therefore I will focus on pediatric head and neck and central nervous system tumors. Summary of Evidence for Pediatric head and neck and central nervous system cancers: Although children often survive their pediatric cancers, the long term morbidity of treatment, including radiation, can have dramatic effects on quality of life, which can be mitigated with proton therapy. Although the impact of radiation late effects is most obvious with central nervous system tumors, many of the same considerations apply when treating	Thank you for your comments.

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		pediatric cancers abutting or close to the central nervous system, such as rhabdomyosarcomas of the face and orbit.	
W	165	Among the many studies of pediatric patients receiving radiation therapy, some of the most relevant include. • Pediatric patients had improved short term morbidity when comparing a cohort of proton-treated patients with historical controls. (1) • Patients receiving irradiation for a brain tumor before than age of four, only a third of adult survivors were able to have full -time employment. (2) Modeling of proton therapy versus photon therapy showed decreased effect on neurocognitive development and pituitary ·function with proton therapy. (3) • Young children with ependymoma treated with protons showed patients exhibited remarkably few side effects in terms of hearing loss, neurocognitive effects, and pituitary dysfunction compared to historical controls. (4) • Children treated with protons for low grade gliomas showed almost no neurocognitive, endocrine or visual effects of the treatment in follow up. (5) • Children with retinoblastoma treated with photon radiation had a 14% 10 year cumulative incidence of secondary malignancies versus 0% in patients treated with protons. (6) • Using protons for craniospinal irradiation is likely to mitigate the future risk of breast cancer, ovarian failure, and hemi disease in adult survivors of embryonal brain tumors. (7-9) • Overall, when including future costs of late effects, *proton therapy will be cost-effective compared to photon therapy* for medulloblastoma. (10) • *Proton therapy will be cost-effective* based on growth hormone function preservation when it reduces dose to the hypothalamus (11)	Reference 1 was published after WAHTA and is a case series of 83 patients 21 years and younger treated 2009-2012, who were compared to historical controls. Authors conclude "In comparison to conventional therapy, patients with particle therapy do not suffer from increased acute treatment-related toxicity during the first months." References 2 and 3 are addressed above; please see comments 61 and 95. Reference 4 is considered in the WAHTA evidence review. Reference 5 was published after the WAHTA review and is a case series of 32 pediatric patients treated from 1995 to 2007. Authors conclude, "Proton RT appears to be associated with good clinical outcome, especially when the tumor location allows for increased sparing of the left temporal lobe, hippocampus, and hypothalamic-pituitary axis." Reference 6 was also published after the WAHTA review and is a retrospective comparative

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			cohort study of 55 proton and 31 photon patients. The 10-year cumulative incidence of RT-induced or in-field second malignancies was significantly different between radiation modalities (0% vs 14%). The 10-year cumulative incidence of all second malignancies was also different, although with borderline significance (5% vs 14%). Reference 7 is a treatment modeling study of six female patients that designed photon and proton beam plans to compare radiation dose to the breast. Dose to breast tissues was near zero after proton therapy to the spine. Reference 8 is another modeling study in which proton therapy is compared to oophoropexy followed by Xray craniospinal irradiation in a single patient. Reference 9 is addressed in comment 59. References 10 and 11 are addressed in comment 13. HTAS recommended coverage of pediatric malignant tumors.
W	166	Thank you for this opportunity. Should you have any questions please do not hesitate to contact me	Thank you for your comments.

ID	#	Comment	Disposition
X	167	Hello, I would like to see Regence cover proton radiation therapy for all forms of cancer, or at least liver cancer where it has proven to be efficacious.	Commenter addresses Regence; nevertheless, thank you for your comments.
Y	168	On behalf of the National Association for Proton Therapy (NAPT), we respectfully submit comments on Oregon's Health Evidence Review Commission (HERC) Coverage Guidance on Proton Beam Therapy (PBT). While we were pleased to see the strong recommendation for coverage of malignant ocular tumors, we have significant concerns with many of the other recommendations. We were especially surprised and disappointed with the lack of a positive coverage recommendation for pediatric malignant tumors. Because of the strong evidence supporting its use, PBT for pediatric patients is practically universally covered. Additionally, we strongly disagree with your characterization that "PBT is far more expensive than its major alternatives." Recent studies have found that when treating for toxicity and other post-treatment occurrences are considered, PBT has been found to be a cost-effective treatment. We urge you to consider the evidence we provide in this letter in your deliberations. Evidence on the Effectiveness of PBT for Pediatric Malignant Tumors The proposed coverage guidance gave a weak recommendation for coverage for pediatric malignant tumors, despite the overwhelming consensus on its appropriateness for pediatric patients. We believe eliminating coverage of PBT for pediatric patients is inconsistent with the current state of evidence and would be harmful to a population of patients who would most benefit from the reduced amount of radiation received in the course of PBT treatment. Due to the growing body of evidence in this area, most payors, regulators and providers support the use of PBT for pediatric patients. The consensus is reflected in the American Society for Radiation Oncology (ASTRO) model policy on PBT which supports its use for primary or benign solid tumors treated in children with curative intent (ASTRO, 2014). Examples of published evidence in this area include a recent study of 54 patients with pediatric rhabdomyosarcoma which found that PBT lowers integral dose and improves sparing normal tissue when compared to IMRT [Ladra, MM et al Radiother Oncol 2014]. In another example, a 2012 study of high-risk pediatric neuroblastoma found that preliminary outcomes reveal excellent control with proton therapy for this population [Hattagangadi JA, Int J Radiat Oncol Biol Phys, 2012]. While we have cited just two studies, these are consistent with other studies of pediatric patients. Evidence on the Effectiveness of PBT for Other Sites The proposed guidance concludes, " ... there was insufficient evidence to obtain even a basic understanding of PBT' s comparative clinical effectiveness and comparative value." Frankly, we were stunned by this characterization. While we acknowledge (and support) the ongoing development of additional clinical evidence, there is already significant evidence supporting the effectiveness of PBT that this proposed coverage guidance ignores. In addition to the evidence	Identical letter to that submitted by commenter P; see responses above

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		supporting the use of PBT for pediatric tumors, there is also significant evidence supporting its use for other tumor sites. The articles listed below are only from the last 15 months and they reflect the meaningful research being conducted in this area. 2015 • Cuaron JJ, Chon B, Tsai H, Goenka A, DeBlois D, Ho A, Simon P, HugE, Cahlon 0 . Early toxicity in patients treated with postoperative proton therapy for locally advanced breast cancer. *Radiation Oncology.* Published online March 6, 2015. • Holliday EB, Mitra HS, Somerson JS, Rhines LD, Mahajan A, Brown PD, Grosshans DR. Postoperative proton therapy for chordomas and chondrosarcomas of the spine: adjuvant vs. salvage radiation therapy. *Spine.* Published online January 23, 2015. • Mizumoto M, Oshiro Y, Takizawa D, Fukushima T, Fukushima H, Yamamoto T, Muroi A, Okumura T, Koji T, Sakura H. Proton beam therapy for pediatric patients with ependymoma. *Pediatrics International.* 2015; DOI:10.1111/ped.12624. • Vega RM, Kim J, Hollander A, Hattangadi-Giuth J, Michalski J, Tarbell NJ, Yock Tl, Bussiere M, MacDonald SM. Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *Cancer.* Published online January 29, 2015. 2014 • Brower *N,* Gans S, Hartsell WF, Goldman S, Fangusaro JR, Patel N, Lulla RR, Smiley NP, Change JH, Gondi V. Proton therapy and helical tomothrapy result in reduced dose deposition to the pancreas in the setting of cranio-spinal irradiation for medulloblastoma: implications for reduced risk of diabetes mellitus in long-term survivors. *Acta Oncol.* 2014 Nov: 1-5. • Frank SJ, Cox JD, Gillin M, Mohan R, Garden AS, Rosenthal DI, Gunn GB, Weber RS, Kies MS, Lewin JS, Munsell MF, Palmer MB, Sahoo N, Zhang X, Liu W, Zhu XR. Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation topractice. *Int J Radiat Oncol Bioi Phys.* 2014 Jul 15;89(4):846-53. • Kesarwala AH, Ko CJ, Ning H, et al. Intensity-modulated proton therapy for elective nodal irradiation and involved-field radiation in the definitive treatment of locally advanced non-smallcell lung cancer: a dosimetric study. *Clinical Lung Cancer.* Available online 9 December 2014. Ladra MM, Szymonifka JD, Mahajan A, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. *J Clin Oncol.* 2014 Oct 20; epub ahead of print. • Ling TC, Slater JM, et al. Analysis of intensity-modulated radiation therapy (IMRT), proton and 3D conformal	

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		you failed to consider these benefits. A study published in *Cancer* [Mailhot Vega, RB et al, *Cancer* 2013] found that by avoiding years of costly side effects, PBT can be cost-effective for children with medulloblastoma. An example of this more comprehensive analysis is a recent study issued by MD Anderson Cancer Center and presented at the October 2014 meeting ofPTCOG-NA (manuscript under development). The study found that the cost of PBT when used for accelerated partial breast irradiation to decrease overall treatment time and toxicity, was estimated at $13,833. Results of the study suggested that the cost of proton therapy is similar to other types of radiation. *NAPT strongly recommends that you include studies that consider cost of toxicity and other post-treatment conditions that can occur and which certainly impact costs and the quality of life of the patient.* While we appreciate the opportunity to submit comments, we felt very limited in our ability to communicate to you due to the severe limitations on written (1000 word) and oral (3 minutes) comments. We believe the current process may stymie public input. *NAPT urges you to reconsider these guidelines.* Should you have any questions, please do not hesitate to contact me	

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